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| <b>(54) Title:</b> EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST AND ANGIOTENSIN II ANTAGONIST COMBINATION THERAPY FOR TREATMENT OF CONGESTIVE HEART FAILURE  |           |   |
| <b>(57) Abstract</b><br><p>A combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist is described for treatment of circulatory disorders, including cardiovascular disorders such as hypertension, congestive heart failure, cirrhosis and ascites. Preferred angiotensin II receptor antagonists are those compounds having high potency and bioavailability and which are characterized in having an imidazole or triazole moiety attached to a biphenylmethyl or pyridinyl/phenylmethyl moiety. Preferred epoxy-steroidal aldosterone receptor antagonists are 20-spiroxane steroidal compounds characterized by the presence of 9<math>\alpha</math>, 11<math>\alpha</math>-substituted epoxy moiety. A preferred combination therapy includes the angiotensin II receptor antagonist 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl]-1H-tetrazole and the aldosterone receptor antagonist epoxymexrenone.</p> |           |   |

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EPOXY-STEROIDAL ALDOSTERONE ANTAGONIST AND  
ANGIOTENSIN II ANTAGONIST COMBINATION THERAPY FOR  
TREATMENT OF CONGESTIVE HEART FAILURE

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Field of the Invention

Combinations of an epoxy-steroidal aldosterone  
receptor antagonist and an angiotensin II receptor  
10 antagonist are described for use in treatment of circulatory  
disorders, including cardiovascular diseases such as  
hypertension, congestive heart failure, cardiac hypertrophy,  
cirrhosis and ascites. Of particular interest are therapies  
using an epoxy-containing steroidal aldosterone receptor  
15 antagonist compound such as epoxymexrenone in combination  
with an angiotensin II receptor antagonist compound.

Background of the Invention

20 Myocardial (or cardiac) failure, whether a  
consequence of a previous myocardial infarction, heart  
disease associated with hypertension, or primary  
cardiomyopathy, is a major health problem of worldwide  
proportions. The incidence of symptomatic heart failure has  
25 risen steadily over the past several decades.

In clinical terms, decompensated cardiac failure  
consists of a constellation of signs and symptoms that  
arises from congested organs and hypoperfused tissues to  
30 form the congestive heart failure (CHF) syndrome.  
Congestion is caused largely by increased venous pressure  
and by inadequate sodium ( $\text{Na}^+$ ) excretion, relative to dietary  
 $\text{Na}^+$  intake, and is importantly related to circulating levels  
of aldosterone (ALDO). An abnormal retention of  $\text{Na}^+$  occurs  
35 via tubular epithelial cells throughout the nephron,  
including the later portion of the distal tubule and  
cortical collecting ducts, where ALDO receptor sites are  
present.

ALDO is the body's most potent mineralocorticoid hormone. As connoted by the term mineralocorticoid, this steroid hormone has mineral-regulating activity. It promotes  $\text{Na}^+$  reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive tissues. ALDO regulates  $\text{Na}^+$  and water resorption at the expense of potassium ( $\text{K}^+$ ) and magnesium ( $\text{Mg}^{2+}$ ) excretion.

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ALDO can also provoke responses in nonepithelial cells. Elicited by a chronic elevation in plasma ALDO level that is inappropriate relative to dietary  $\text{Na}^+$  intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as non-renin-dependent factors (such as  $\text{K}^+$ , ACTH) that promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine its plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

The renin-angiotensin-aldosterone system (RAAS) is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension. Activation of the renin-angiotensin-aldosterone system begins with renin secretion from the juxtaglomerular cells in the kidney and culminates in the formation of angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects such as stimulating aldosterone secretion, promoting



sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic effect and modulating other hormonal systems.

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Previous studies have shown that antagonizing angiotensin II binding at its receptors is a viable approach to inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such peptidic compounds are of limited use due to their lack of oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

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Non-peptidic compounds with angiotensin II antagonist properties are known. For example, early descriptions of such non-peptidic compounds include the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid which has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and *in vivo* tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247(1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and *in vivo* tests [A. T. Chiu et al, European J. Pharmacol., 157, 31-21 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250(3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives

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useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant decrease in mean arterial blood pressure in conscious

5 hypertensive rats. Other families of non-peptidic angiotensin II antagonists have been characterized by molecules having a biphenylmethyl moiety attached to a heterocyclic moiety. For example, EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole

10 compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles,

15 biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole. U.S. Patent No. 4,880,804 to Carini et al describes a family of biphenylmethylbenzimidazole compounds

20 as angiotensin II receptor blockers for use in treatment of hypertension and congestive heart failure.

Many aldosterone receptor blocking drugs are known. For example, spironolactone is a drug which acts at

25 the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary

30 hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosterone-related diseases such as liver cirrhosis and congestive heart failure [F.J. Saunders et al, Aldactone:

35 Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day] were administered to a spironolactone-intolerant

patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug, 1986)]. It has been recognized that development of myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to excessive collagen deposition [D. Klug et al, Am. J. Cardiol., 71 (3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G. Brilla et al, J. Mol. Cell. Cardiol., 25(5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)].

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Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

30

Moreover, although ACE inhibitors effectively block the formation of angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, J. Endocrinol., 91, 457-465 (1981)]. A similar effect has been observed for patients with myocardial infarction receiving zofenopril [C. Borghi

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et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. This phenomenon has been termed "aldosterone escape".

Another series of steroidal-type aldosterone receptor antagonists is exemplified by epoxy-containing spironolactone derivatives. For example, U.S. Patent No. 4,559,332 issued to Grob et al describes 9 $\alpha$ ,11 $\alpha$ -epoxy-containing spironolactone derivatives as aldosterone antagonists useful as diuretics. These 9 $\alpha$ ,11 $\alpha$ -epoxy steroids have been evaluated for endocrine effects in comparison to spironolactone [M. de Gasparo et al, J. Pharm. Exp. Ther., 240(2), 650-656 (1987)].

Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and that aldosterone levels increase as CHF progresses from activation of the Renin-Angiotensin-Aldosterone System (RAAS). Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. Cardiol., 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of captopril and spironolactone was administered and found effective to control refractory CHF without serious incidents of hyperkalemia [U. Dahlstrom et al, Am. J. Cardiol., 71, 29A-33A (21 Jan 1993)]. Spironolactone coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure [A.A. van Vliet et al, Am. J. Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements

have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)].

Combinations of an angiotensin II receptor antagonist and aldosterone receptor antagonist, are known. For example, PCT Application No. US91/09362 published 25 June 1992 describes treatment of hypertension using a combination of an imidazole-containing angiotensin II antagonist compound and a diuretic such as spironolactone.

Summary of the Invention

A combination therapy comprising a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist and a therapeutically-effective amount of an angiotensin II receptor antagonist is useful to treat circulatory disorders, including cardiovascular disorders such as hypertension, congestive heart failure, cirrhosis and ascites.

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The phrase "angiotensin II receptor antagonist" is intended to embrace one or more compounds or agents having the ability to interact with a receptor site located on various human body tissues, which site is a receptor having a relatively high affinity for angiotensin II and which receptor site is associated with mediating one or more biological functions or events such as vasoconstriction or vasorelaxation, kidney-mediated sodium and fluid retention, sympathetic nervous system activity, and in modulating secretion of various substances such as aldosterone, vasopressin and renin, to lower blood pressure in a subject susceptible to or afflicted with elevated blood pressure. Interactions of such angiotensin II receptor antagonist with this receptor site may be characterized as being either "competitive" (i.e., "surmountable") or as being "insurmountable". These terms, "competitive" and "insurmountable", characterize the relative rates, faster for the former term and slower for the latter term, at which the antagonist compound dissociates from binding with the receptor site.

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The phrase "epoxy-steroidal aldosterone receptor antagonist" is intended to embrace one or more agents or compounds characterized by a steroid-type nucleus and having an epoxy moiety attached to the nucleus and which agent or compound binds to the aldosterone receptor, as a competitive inhibitor of the action of aldosterone itself at the receptor site, so as to modulate the receptor-mediated

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activity of aldosterone.

The phrase "combination therapy", in defining use of an angiotensin II antagonist and an epoxy-steroidal aldosterone receptor antagonist, is intended to embrace administration of each antagonist in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended to embrace co-administration of the antagonist agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each antagonist agent.

The phrase "therapeutically-effective" is intended to qualify the amount of each antagonist agent for use in the combination therapy which will achieve the goal of reduction of hypertension with improvement in cardiac sufficiency by reducing or preventing, for example, the progression of congestive heart failure.

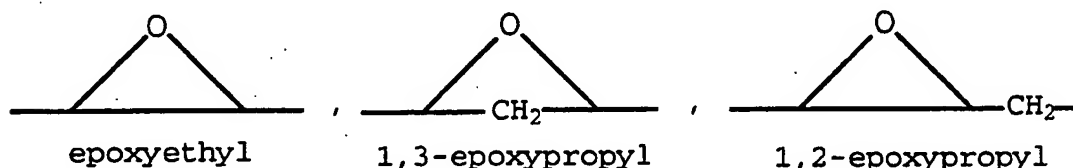
Another combination therapy of interest would consist essentially of three active agents, namely, an AII antagonist, an aldosterone receptor antagonist agent and a diuretic.

For a combination of AII antagonist agent and an ALDO antagonist agent, the agents would be used in combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of the AII antagonist agent to the aldosterone receptor antagonist agent. A preferred range of these two agents (AII antagonist-to-ALDO antagonist) would be from about one-to-one to about fifteen-to-one, while a more preferred range would be from about one-to-one to about five-to-one, depending ultimately on the selection of the AII antagonist and ALDO antagonist. The diuretic agent may be present in a ratio range of 0.1-to-one to about ten to one (AII antagonist to diuretic).

Detailed Description of the Invention

Epoxy-steroidal aldosterone receptor antagonist compounds suitable for use in the combination therapy consist of these compounds having a steroidal nucleus substituted with an epoxy-type moiety. The term "epoxy-type" moiety is intended to embrace any moiety characterized in having an oxygen atom as a bridge between two carbon atoms, examples of which include the following moieties:

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The term "steroidal", as used in the phrase "epoxy-steroidal", denotes a nucleus provided by a cyclopentenophenanthrene moiety, having the conventional "A", "B", "C" and "D" rings. The epoxy-type moiety may be attached to the cyclopentenophenanthrene nucleus at any attachable or substitutable positions, that is, fused to one of the rings of the steroidal nucleus or the moiety may be substituted on a ring member of the ring system. The phrase "epoxy-steroidal" is intended to embrace a steroidal nucleus having one or a plurality of epoxy-type moieties attached thereto.

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Epoxy-steroidal aldosterone receptor antagonists suitable for use in combination therapy include a family of compounds having an epoxy moiety fused to the "C" ring of the steroidal nucleus. Especially preferred are 20-spiroxane compounds characterized by the presence of a 9 $\alpha$ ,11 $\alpha$ -substituted epoxy moiety. Table I, below, describes a series of 9 $\alpha$ ,11 $\alpha$ -epoxy-steroidal compounds which may be used in the combination therapy. These epoxy steroids may be prepared by procedures described in U.S. Patent No. 4,559,332 to Grob et al issued 17 December 1985.



TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name   |
|------------|-----------|--|
| 1          |           | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, $\gamma$ -lactone, methyl ester, (7 $\alpha$ ,11. $\alpha$ .,17 $\alpha$ ) - |
| 2          |           | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ ) -                      |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name   |
|------------|-----------|--|
| 3          |           | 3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ -lactone, (6 $\beta$ ,7 $\beta$ ,11 $\beta$ ,17 $\beta$ )- |
| 4          |           | Pregn-4-ene-7,21-dicarboxylic acid,9,11-epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt, (7a,11a,17a)-   |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name   |
|------------|-----------|--|
| 5          |           | Pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7a,11a,17a)-         |
| 6          |           | 3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g-lactone (6a,7a,11.a) - |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name   |
|------------|-----------|--|
| 7          |           | 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6a,7a,11a,17a)-       |
| 8          |           | 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6a,7a,11a,17a)- |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name   |
|------------|-----------|--|
| 9          |           | 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,g-lactone, (6a,7a,11a.,17a) - |
| 10         |           | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, ethyl ester, (7a,11a,17a) -                        |

TABLE I: Aldosterone Receptor Antagonist

| Compound # | Structure | Name  |
|------------|-----------|---|
| 11         |           | Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,g-lactone, 1-methylethyl ester, (7a,11a,17a) - |

Angiotensin II receptor antagonist compounds suitable for use in the combination therapy are described in Table II, below. Preferred compounds for use in the combination therapy may be generally characterized structurally as having two portions. A first portion constitutes a mono-aryl-alkyl moiety, or a bi-aryl-alkyl moiety, or a mono-heteroaryl-alkyl moiety, or a bi-heteroaryl-alkyl moiety. A second portion constitutes a heterocyclic moiety or an open chain hetero-atom-containing moiety.

Typically, the first-portion mono/bi-aryl/heteroaryl-alkyl moiety is attached to the second portion heterocyclic/open-chain moiety through the alkyl group of the mono/bi-aryl/heteroaryl-alkyl moiety to any substitutable position on the heterocyclic/open-chain moiety second portion. Suitable first-portion mono/bi-aryl/heteroaryl-alkyl moieties are defined by any of the various moieties listed under Formula I:

Ar-Alk-L  
Ar-L-Ar-Alk-L  
Het-L-Ar-Alk-L  
Het-L-Het-Alk-L (I)  
Ar-L-Het-Alk-L  
Het-L-Alk-L

wherein the abbreviated notation used in the moieties of Formula I is defined as follows:

"Ar" means a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being typically fully unsaturated but which also may be partially or fully saturated. "Phenyl" radical most typically exemplifies "Ar".

"Het" means a monocyclic or bicyclic fused ring

system having from five to eleven ring members, and having at least one of such ring members being a hetero atom selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as  
5 ring members.

"Alk" means an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms. Typically, "Alk" means "methylene", i.e., -CH<sub>2</sub>-.

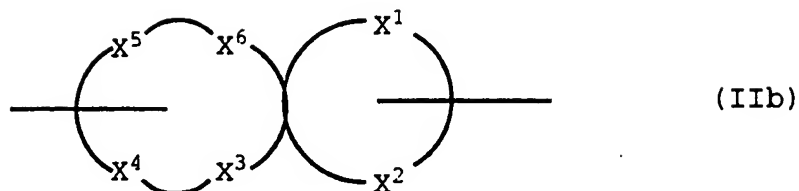
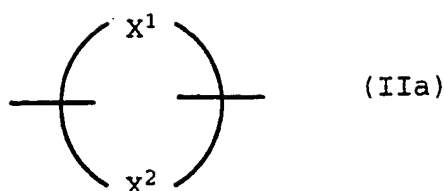
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"L" designates a single bond or a bivalent linker moiety selected from carbon, oxygen and sulfur. When "L" is carbon, such carbon has two hydrido atoms attached thereto.

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Suitable second-portion heterocyclic moieties of the angiotensin II antagonist compounds, for use in the combination therapy, are defined by any of the various moieties listed under Formula IIa or IIb:





wherein each of  $X^1$  through  $X^6$  is selected from  $-\text{CH}=$ ,  $-\text{CH}_2-$ ,  
 5  $-\text{N}=$ ,  $-\text{NH}-$ ,  $\text{O}$ , and  $\text{S}$ , with the proviso that at least one of  
 $X^1$  through  $X^6$  in each of Formula IIa and Formula IIb must be  
 a hetero atom. The heterocyclic moiety of Formula IIa or  
 IIb may be attached through a bond from any ring member of  
 the Formula IIa or IIb heterocyclic moiety having a  
 10 substitutable or a bond-forming position.

Examples of monocyclic heterocyclic moieties of  
 Formula IIa include thienyl, furyl, pyranal, pyrrolyl,  
 imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl,  
 15 pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl,  
 furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl,  
 isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-  
 triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl,  
 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl,  
 20 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,  
 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-  
 dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-  
 dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranal,  
 1,4-pyranal, 1,2-pyranyl, 1,4-pyranyl, pyridinyl,  
 25 piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-  
 oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl, 1,2,6-oxazinyl,  
 1,4-oxazinyl, *o*-isoxazinyl, *p*-isoxazinyl, 1,2,5-  
 oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl,

1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

Examples of bicyclic heterocyclic moieties of

- 5 Formula IIB include benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl,  
10 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiololo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and  
15 4H-1,3-dioxolo[4,5-d]imidazolyl.

- The angiotensin II receptor antagonist compounds, as provided by the first-and-second-portion moieties of Formula I and II, are further characterized by an acidic  
20 moiety attached to either of said first-and-second-portion moieties. Preferably this acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

- 25  $-U_nA$  (III)

- wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide,  
30 ester and salt derivatives of said acidic moieties; wherein U is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms.

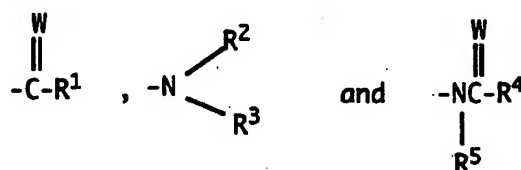
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The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the  $-U_nA$

moiety, is intended to embrace chemical groups which, when attached to any substitutable position of the Formula I-IIa/b moiety, confers acidic character to the compound of Formula I-IIa/b. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I-IIa/b to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I-IIa/b has a  $pK_a$  in a range from about one to about twelve. More typically, the Formula I-IIa/b compound would have a  $pK_a$  in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group ( $-COOH$ ). Where  $n$  is zero and  $A$  is  $-COOH$ , in the  $-U_nA$  moiety, such carboxyl group would be attached directly to one of the Formula I-IIa/b positions. The Formula I-IIa/b compound may have one  $-U_nA$  moiety attached at one of the Formula I-IIa/b positions, or may have a plurality of such  $-U_nA$  moieties attached at more than one of the Formula I-IIa/b positions. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I-IIa/b may have one or more acidic protons and, therefore, may have one or more  $pK_a$  values. It is preferred, however, that at least one of these  $pK_a$  values of the Formula I-IIa/b compound as conferred by the  $-U_nA$  moiety be in a range from about two to about seven. The  $-U_nA$  moiety may be attached to one of the Formula I-IIa/b positions through any portion of the  $-U_nA$  moiety which results in a Formula I-IIa/b compound being relatively stable and also having a labile or acidic proton to meet the foregoing  $pK_a$  criteria. For example, where the  $-U_nA$  acid moiety is tetrazole, the tetrazole is typically attached at

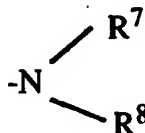
the tetrazole ring carbon atom.

For any of the moieties embraced by Formula I and Formula II, such moieties may be substituted at any  
 5 substitutable position by one or more radicals selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano,  
 10 cyanoamino, nitro, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, aralkoxycarbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl,  
 15 arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



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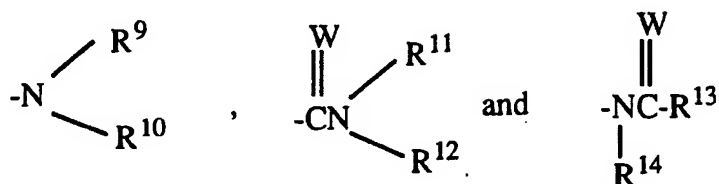
wherein W is oxygen atom or sulfur atom; wherein each of R<sup>1</sup> through R<sup>5</sup> is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR<sup>6</sup> and



25

wherein Y is selected from oxygen atom and sulfur atom and R<sup>6</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>1</sup>, R<sup>2</sup>,  
 30 R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl,

arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is further independently selected from amino and amido radicals of the formula



wherein W is oxygen atom or sulfur atom;  
 wherein each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> is  
 10 independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>2</sup> and R<sup>3</sup> taken together and each of R<sup>4</sup> and R<sup>5</sup> taken together may form a heterocyclic group having five  
 15 to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially  
 20 unsaturated; wherein each of R<sup>2</sup> and R<sup>3</sup> taken together and each of R<sup>7</sup> and R<sup>8</sup> taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more  
 25 hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

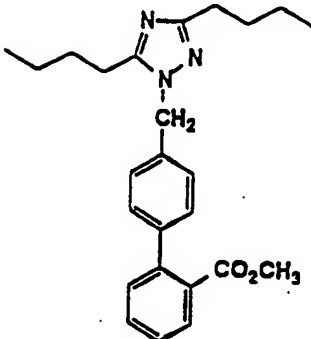
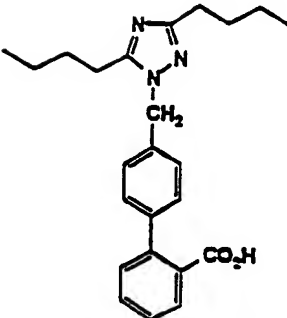
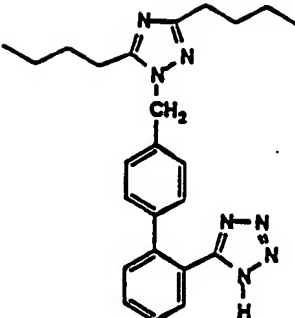
The combination therapy of the invention would be  
 30 useful in treating a variety of circulatory disorders, including cardiovascular disorders, such as hypertension, congestive heart failure, myocardial fibrosis and cardiac hypertrophy. The combination therapy would also be useful with adjunctive therapies. For example, the combination

therapy may be used in combination with other drugs, such as a diuretic, to aid in treatment of hypertension.

Table II, below, contains description of  
5 angiotensin II antagonist compounds which may be used in the  
combination therapy. Associated with each compound listed  
in Table II is a published patent document describing the  
chemical preparation of the angiotensin II antagonist  
compound as well as the biological properties of such  
10 compound. The content of each of these patent documents is  
incorporated herein by reference.

25

TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
|            |    | WO #91/17148<br>pub. 14 Nov 91 |
| 2          |   | WO #91/17148<br>pub. 14 Nov 91 |
| 3          |  | WO #91/17148<br>pub. 14 Nov 91 |

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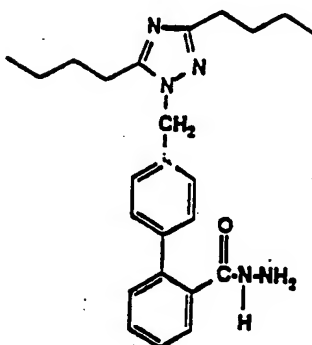
TABLE II: Angiotensin II Antagonists

Compound #

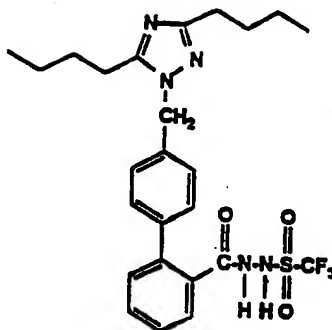
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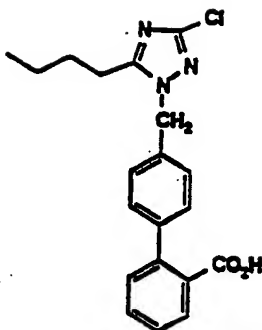
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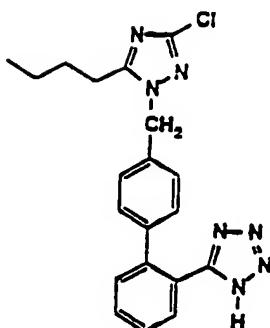
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TABLE II: Angiotensin II Antagonists

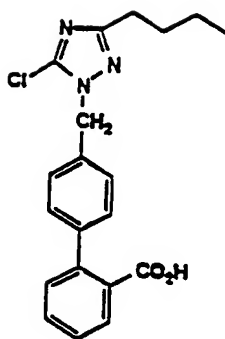
Compound #

Structure

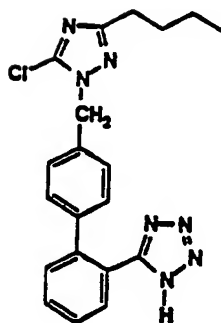
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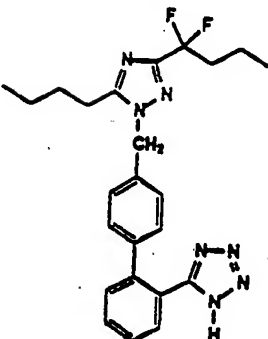
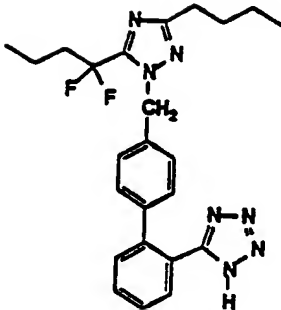
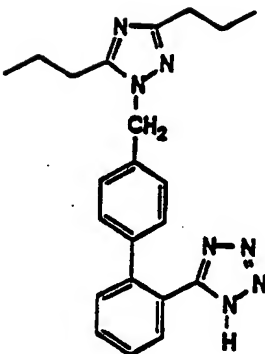
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 10         |    | WO #91/17148<br>pub. 14 Nov 91 |
| 11         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 12         |  | WO #91/17148<br>pub. 14 Nov 91 |

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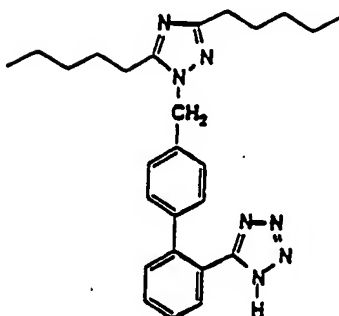
TABLE II: Angiotensin II Antagonists

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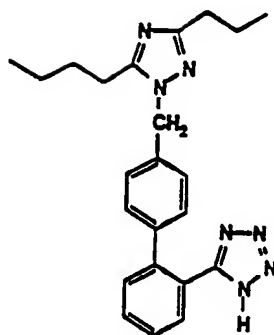
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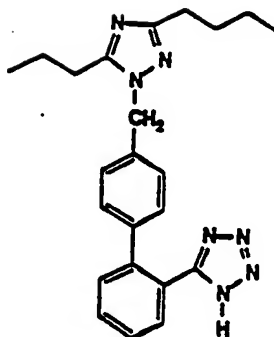
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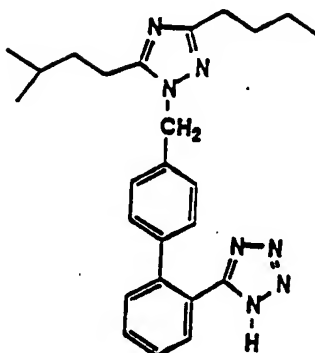
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TABLE II: Angiotensin II Antagonists

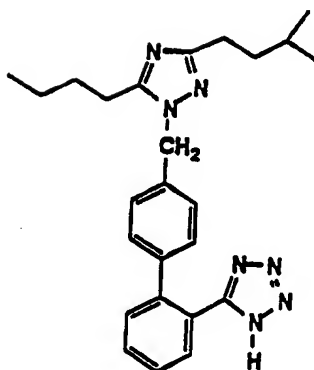
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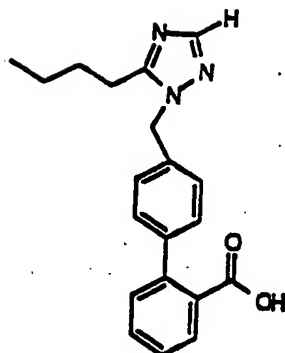
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TABLE II: Angiotensin II Antagonists

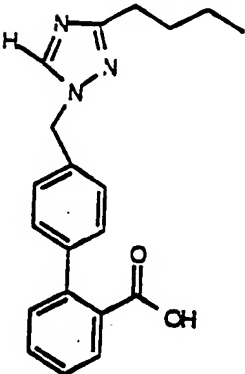
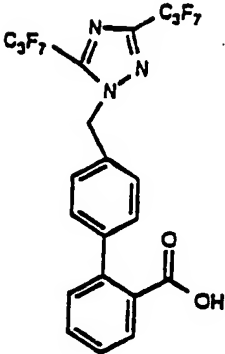
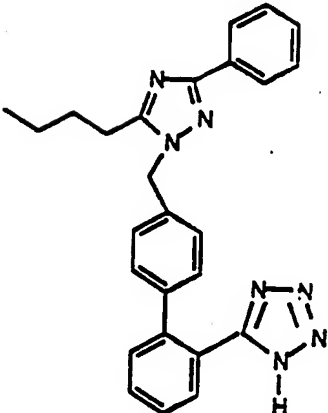
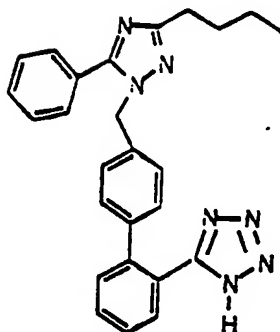
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|------------|---|--------------------------------|
| 19         |    | WO #91/17148<br>pub. 14 Nov 91 |
| 20         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 21         |  | WO #91/17148<br>pub. 14 Nov 91 |

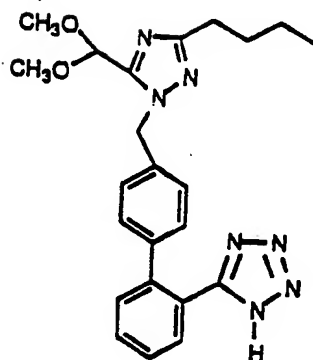
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
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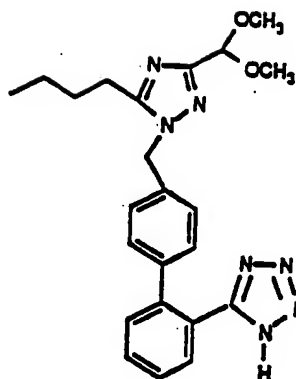
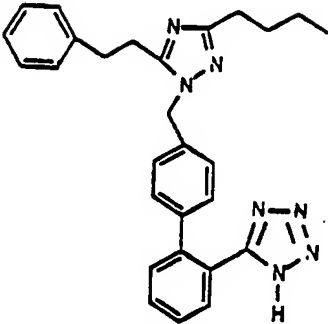
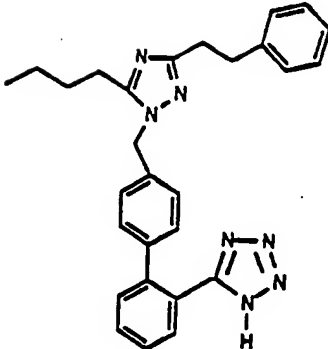
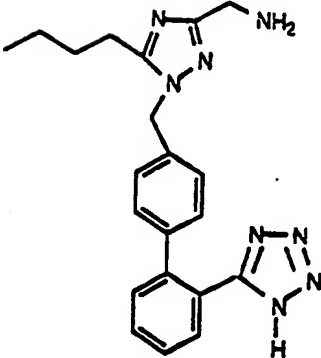
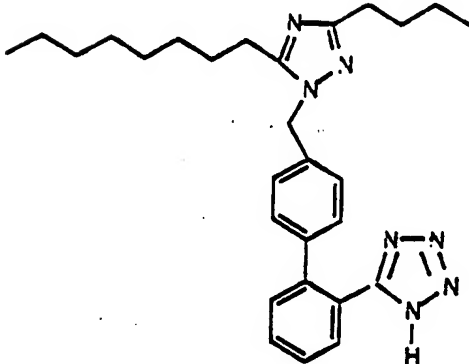
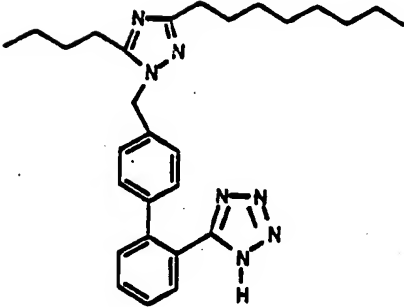
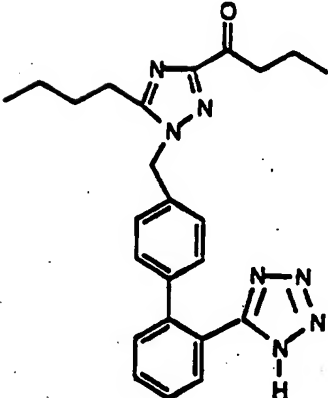
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 25         |    | WO #91/17148<br>pub. 14 Nov 91 |
| 26         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 27         |  | WO #91/17148<br>pub. 14 Nov 91 |

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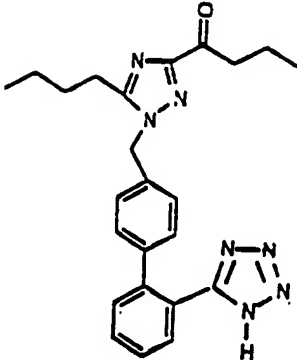
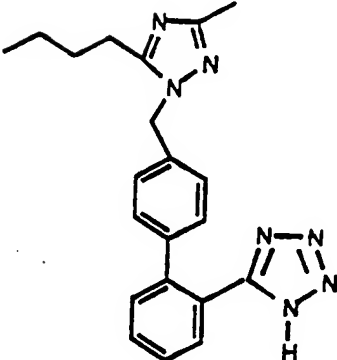
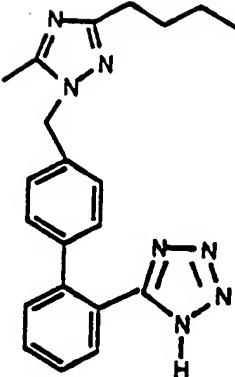
TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 28         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 29         |  | WO #91/17148<br>pub. 14 Nov 91 |
| 30         |  | WO #91/17148<br>pub. 14 Nov 91 |



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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 31         |    | WO #91/17148<br>pub. 14 Nov 91 |
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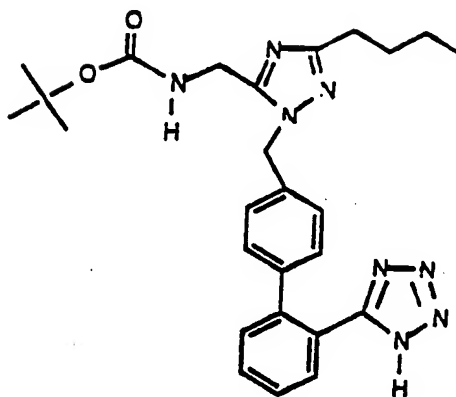
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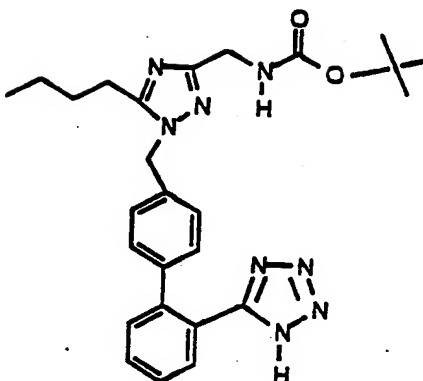
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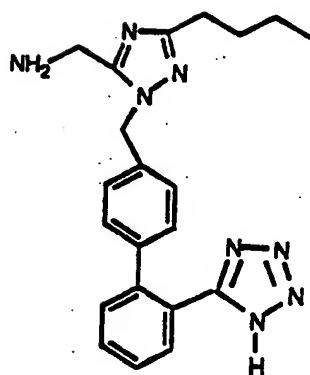
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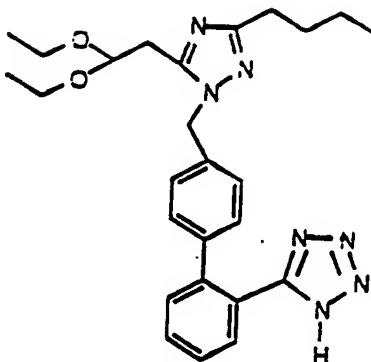
TABLE II: Angiotensin II Antagonists

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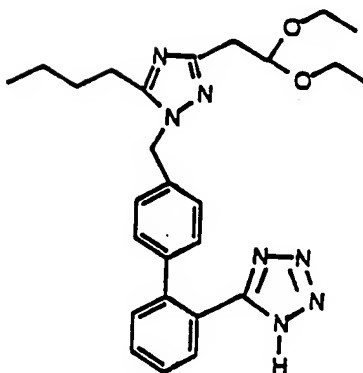
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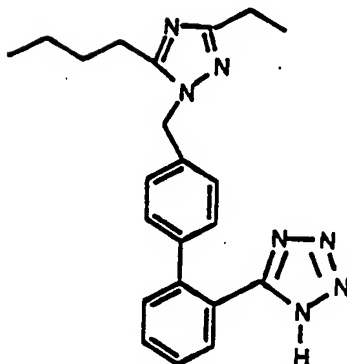
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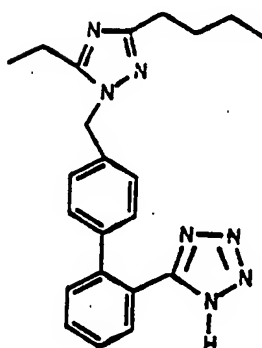
TABLE II: Angiotensin II Antagonists

Compound #

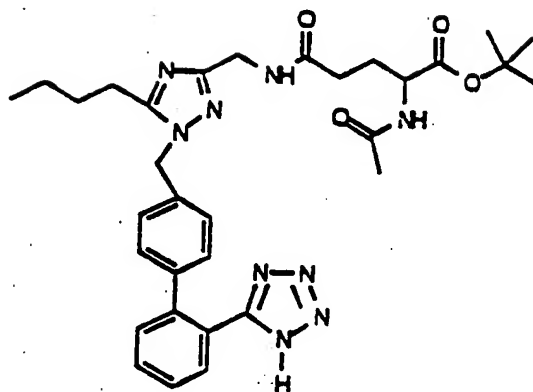
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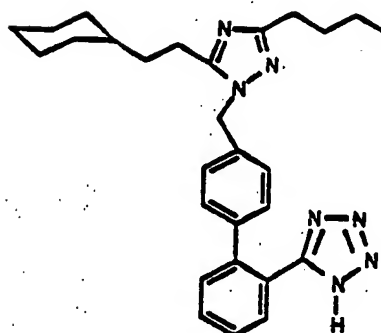
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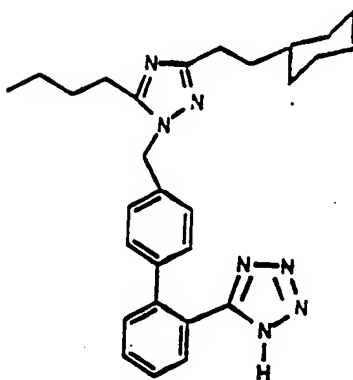
TABLE II: Angiotensin II Antagonists

Compound #

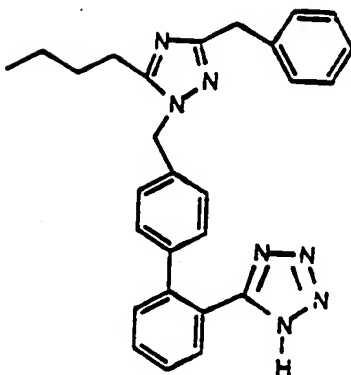
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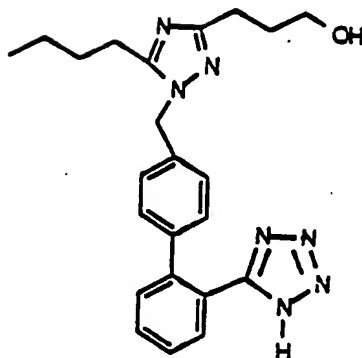
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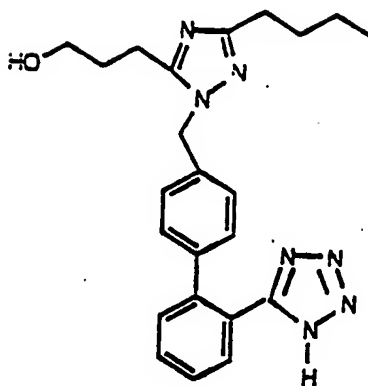
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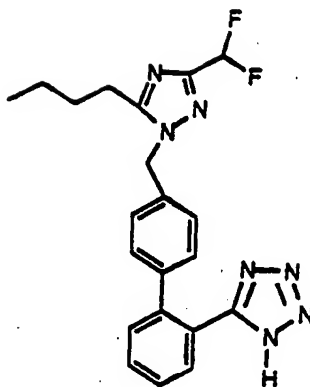
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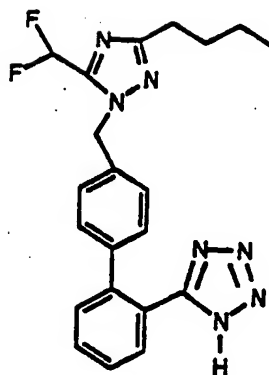
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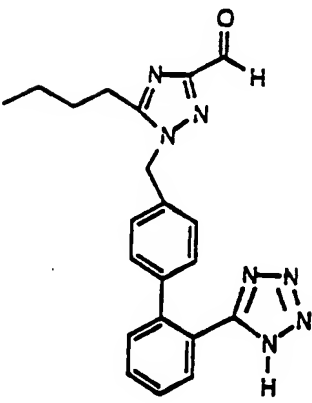
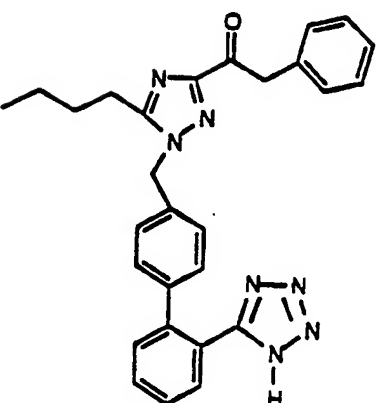
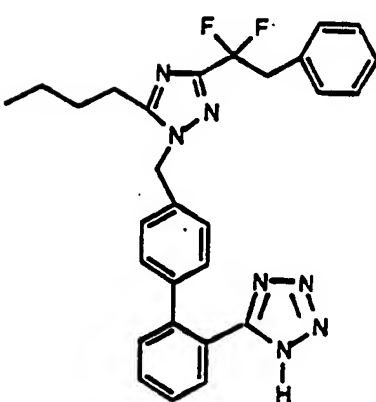
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 49         |    | WO #91/17148<br>pub. 14 Nov 91 |
| 50         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 51         |  | WO #91/17148<br>pub. 14 Nov 91 |

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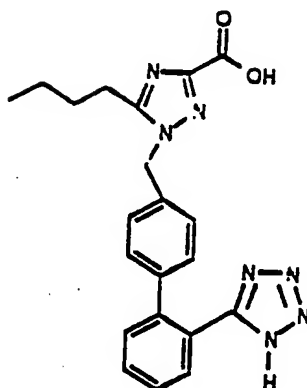
TABLE II: Angiotensin II Antagonists

Compound #

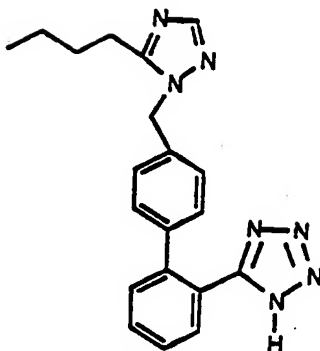
Structure

Source

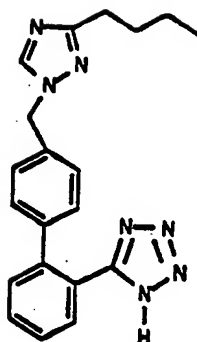
52

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53

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54

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pub. 14 Nov 91







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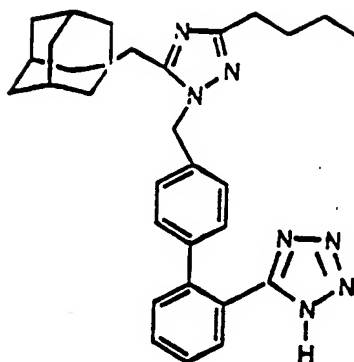
TABLE II: Angiotensin II Antagonists

Compound #

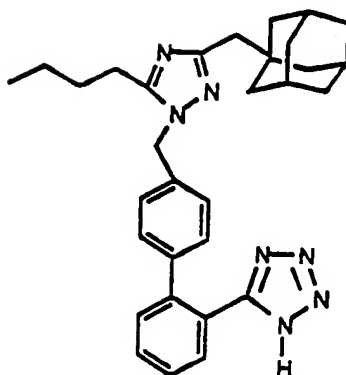
Structure

Source

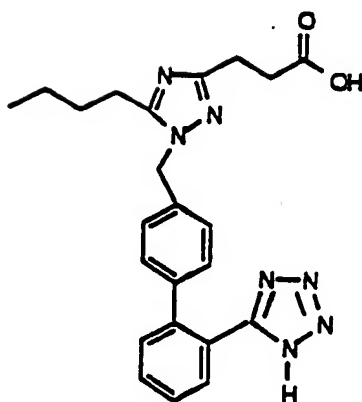
61

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62

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63

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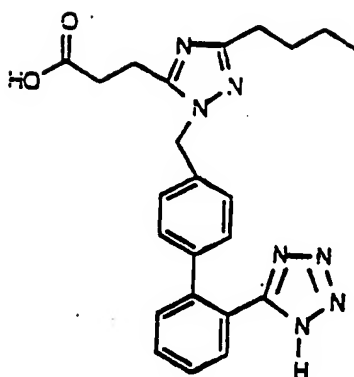
TABLE II: Angiotensin II Antagonists

Compound #

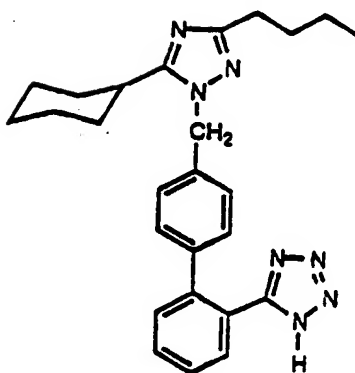
Structure

Source

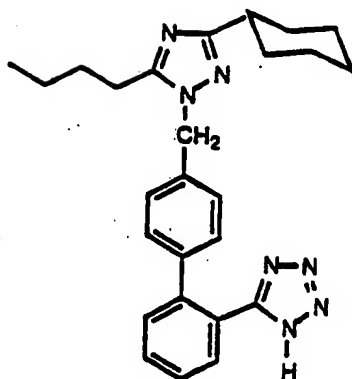
64

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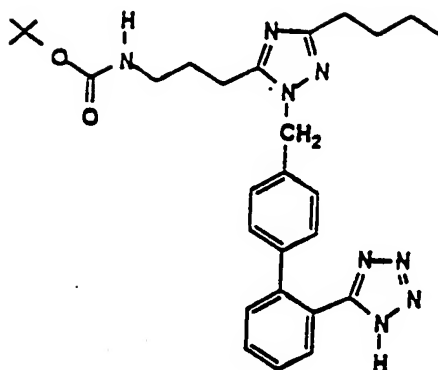
TABLE II: Angiotensin II Antagonists

Compound #

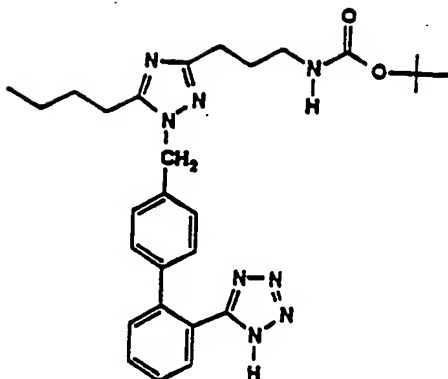
Structure

Source

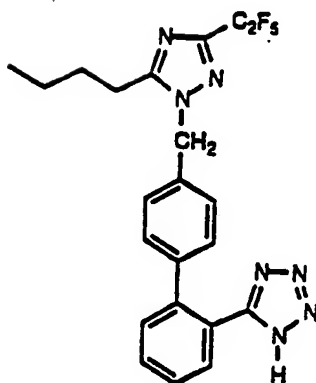
67

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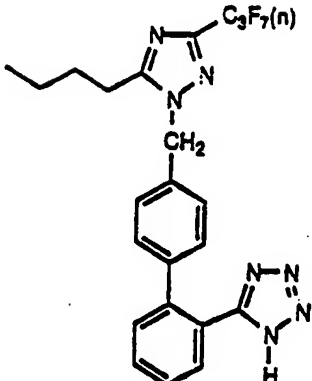
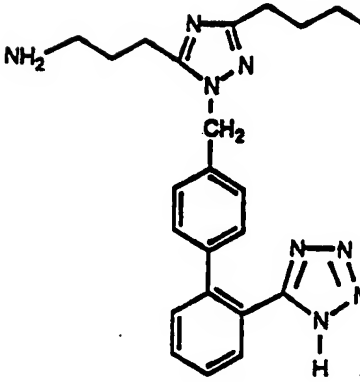
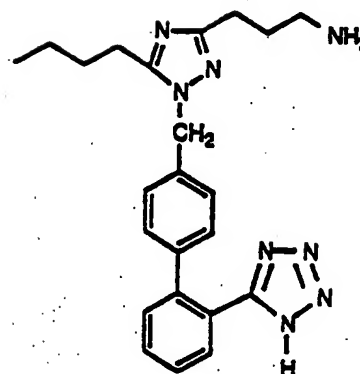
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 70         |    | WO #91/17148<br>pub. 14 Nov 91 |
| 71         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 72         |  | WO #91/17148<br>pub. 14 Nov 91 |

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TABLE II: Angiotensin II Antagonists

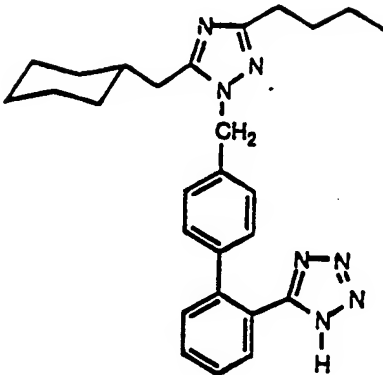
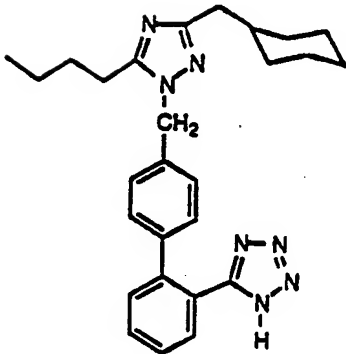
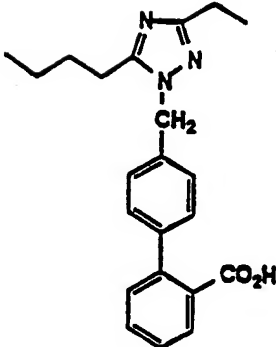
| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 73         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 74         |   | WO #91/17148<br>pub. 14 Nov 91 |
| 75         |  | WO #91/17148<br>pub. 14 Nov 91 |

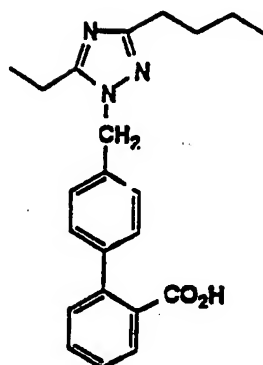
TABLE II: Angiotensin II Antagonists

Compound #

Structure

Source

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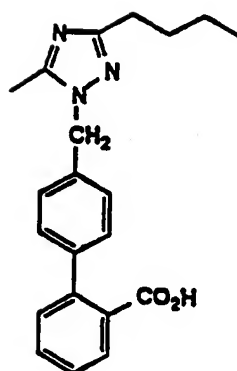
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pub. 14 Nov 91



TABLE II: Angiotensin II Antagonists

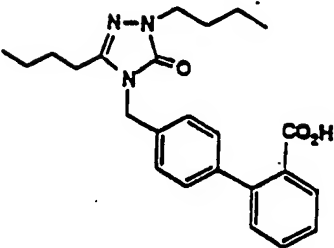
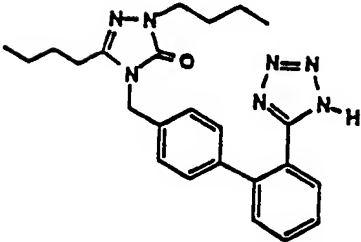
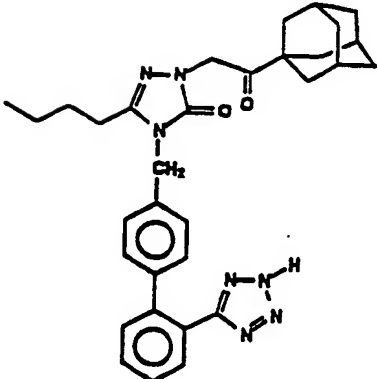
| Compound # | Structure   | Source               |
|------------|---|----------------------|
| 78         |    | WO #91/18888<br>pub. |
| 79         |   | WO #91/18888<br>pub. |
| 80         |  | WO #91/18888<br>pub. |

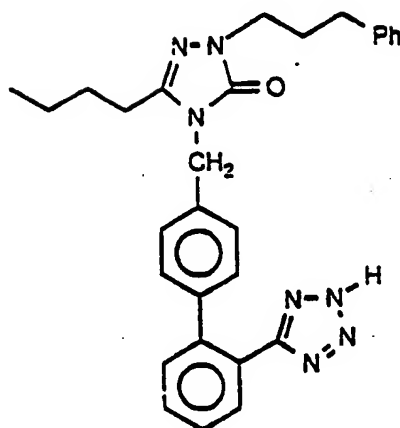
TABLE II: Angiotensin II Antagonists

Compound #

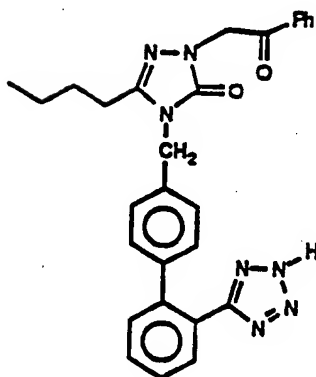
Structure

Source

81

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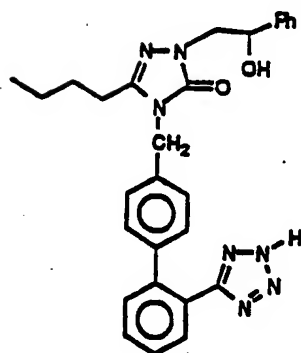
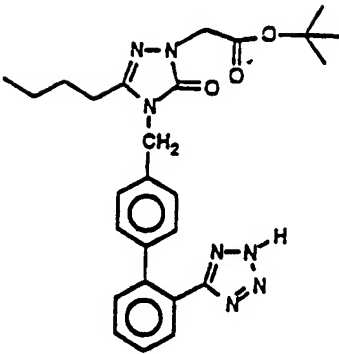
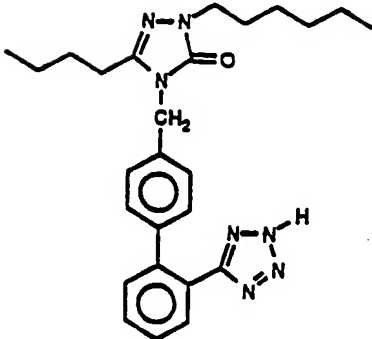
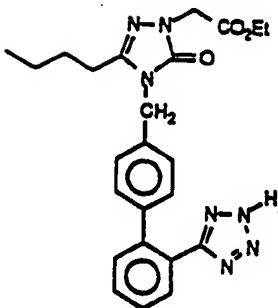
WO #91/18888  
pub.

TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source               |
|------------|---|----------------------|
| 84         |    | WO #91/18888<br>pub. |
| 85         |   | WO #91/18888<br>pub. |
| 86         |  | WO #91/18888<br>pub. |



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TABLE II: Angiotensin II Antagonists

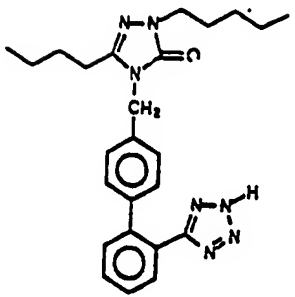
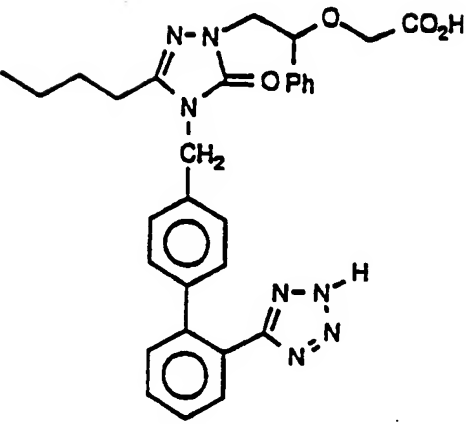
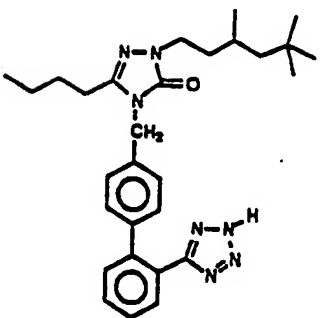
| Compound # | Structure   | Source               |
|------------|---|----------------------|
| 90         |    | WO #91/18888<br>pub. |
| 91         |  | WO #91/18888<br>pub. |
| 92         |  | WO #91/18888<br>pub. |

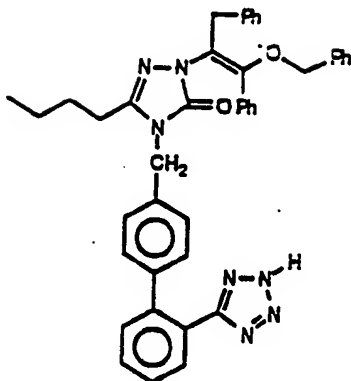
TABLE II: Angiotensin II Antagonists

Compound #

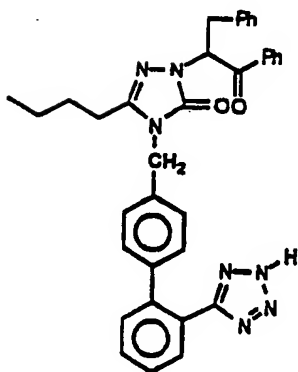
Structure

Source

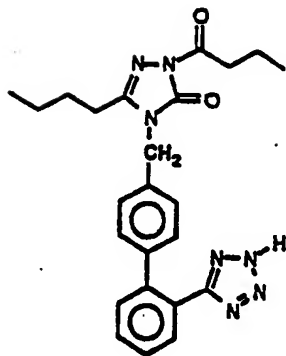
93

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pub.

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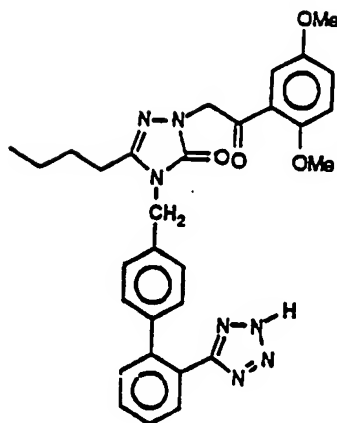
TABLE II: Angiotensin II Antagonists

Compound #

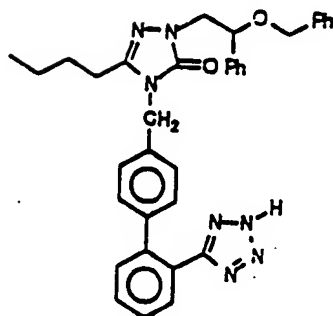
Structure

Source

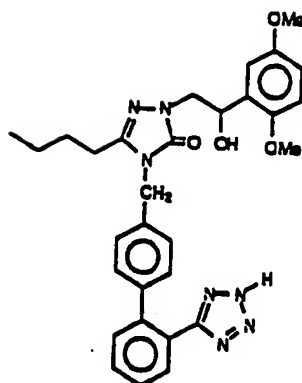
96

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pub.

97

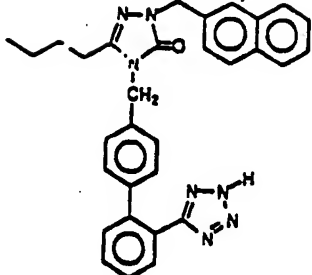
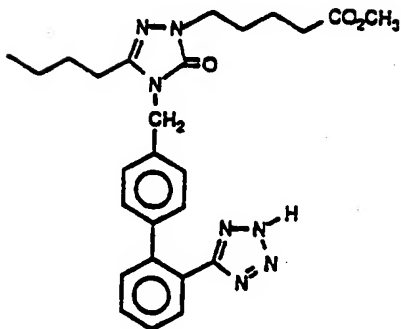
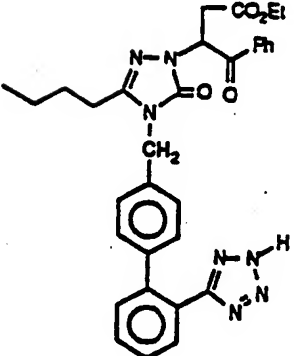
WO #91/18888  
pub.

98

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pub.

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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source               |
|------------|---|----------------------|
| 99         |    | WO #91/18888<br>pub. |
| 100        |  | WO #91/18888<br>pub. |
| 101        |  | WO #91/18888<br>pub. |



**TABLE II:** Angiotensin II Antagonists

| Compound # | Structure | Source               |
|------------|-----------|----------------------|
| 102        |           | WO #91/18888<br>pub. |
| 103        |           | WO #91/18888<br>pub. |
| 104        |           | WO #91/18888<br>pub. |

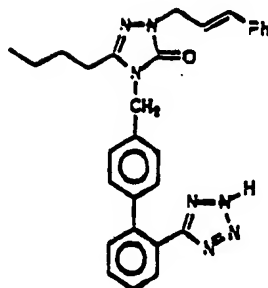
TABLE II: Angiotensin II Antagonists

Compound #

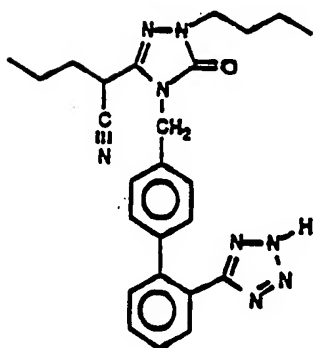
Structure

Source

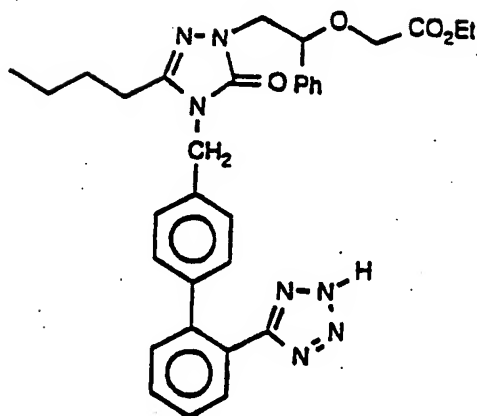
105

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pub.

106

WO #91/18888  
pub.

107

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pub.

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TABLE II: Angiotensin II Antagonists

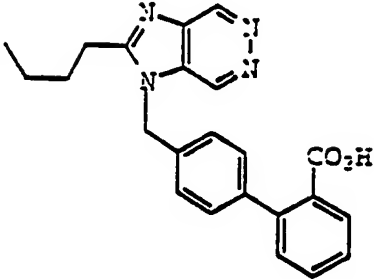
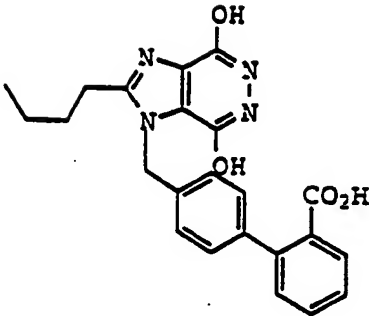
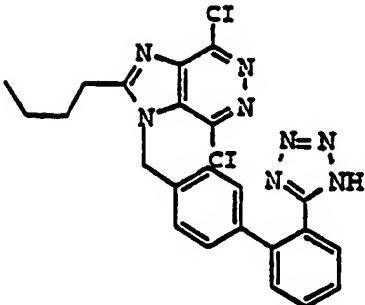
| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 108        |    | WO #91/19715<br>pub. 26 Dec 91 |
| 109        |   | WO #91/19715<br>pub. 26 Dec 91 |
| 110        |  | WO #91/19715<br>pub. 26 Dec 91 |

TABLE II: Angiotensin II Antagonists

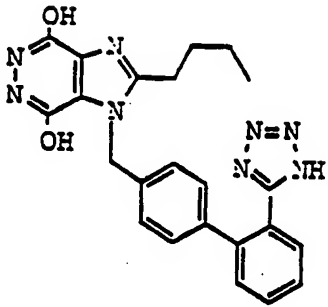
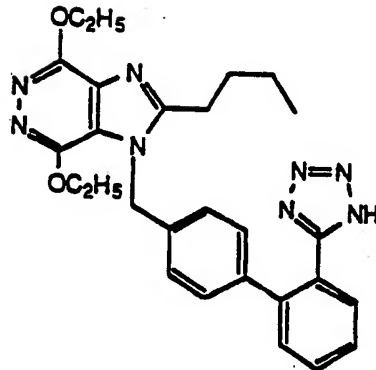
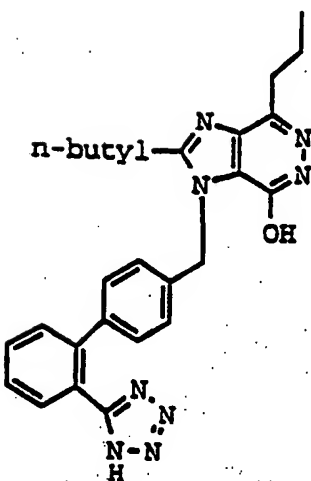
| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 111        |    | WO #91/19715<br>pub. 26 Dec 91 |
| 112        |   | WO #91/19715<br>pub. 26 Dec 91 |
| 113        |  | WO #91/19715<br>pub. 26 Dec 91 |

TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                         |
|------------|--|--------------------------------|
| 114        | <br><chem>CCCC1=CN=C(C1)C(C2=CC=CC=C2C3=NNC=N3)CN=[N+]=[N-]</chem> | WO #91/19715<br>pub. 26 Dec 91 |
| 115        | <br><chem>CCCC1=CN=C(C1)C(C2=CC=CC=C2C3=NNC=N3)CN=[N+]=[N-]</chem> | WO #91/19715<br>pub. 26 Dec 91 |
| 116        | <br><chem>CCCC1=CN=C(C1)C(C2=CC=CC=C2C3=NNC=N3)CN=[N+]=[N-]</chem> | WO #91/19715<br>pub. 26 Dec 91 |

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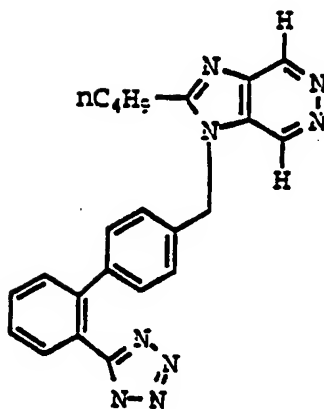
TABLE II: Angiotensin II Antagonists

Compound #

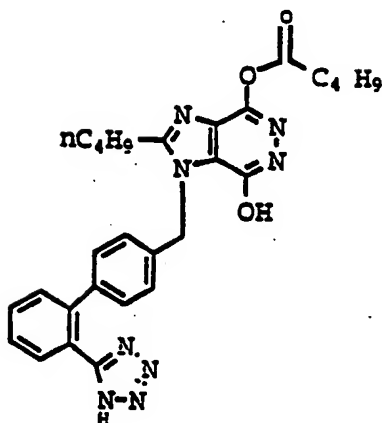
Structure

Source

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119

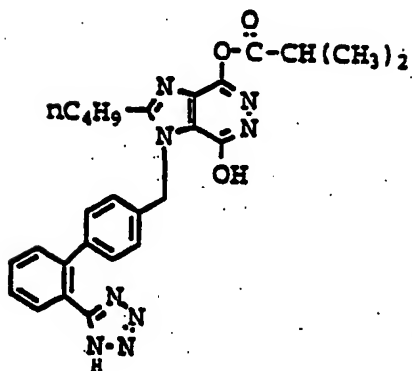
WO #91/19715  
pub. 26 Dec 91

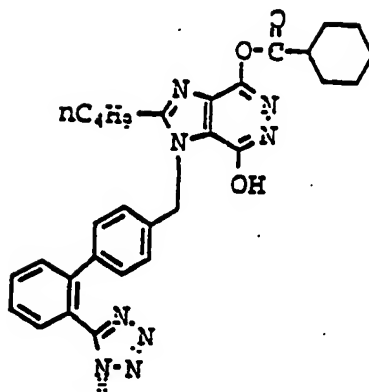
TABLE II: Angiotensin II Antagonists

Compound #

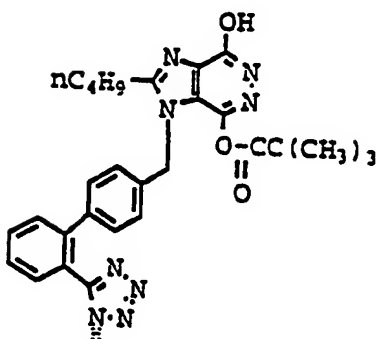
Structure

Source

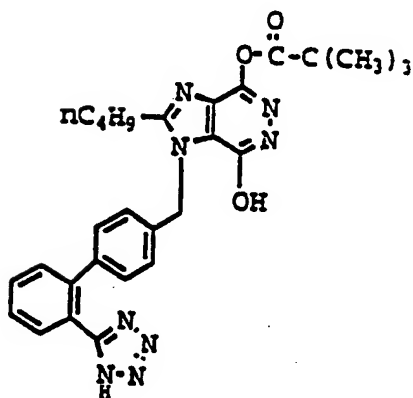
120

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pub. 26 Dec 91

121

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pub. 26 Dec 91

122

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pub. 26 Dec 91

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TABLE II: Angiotensin II Antagonists

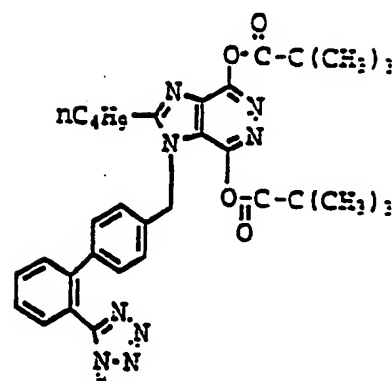
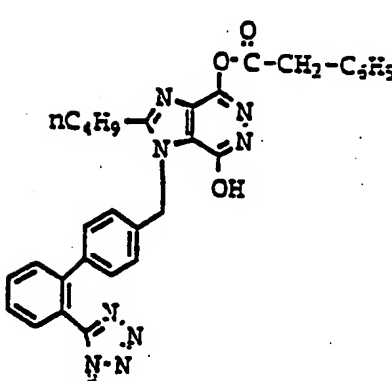
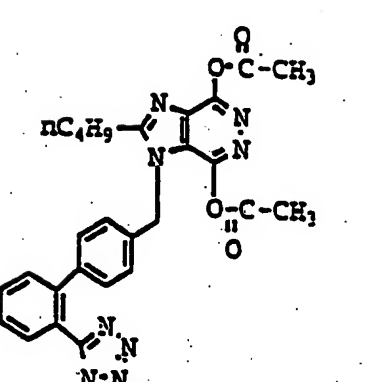
| Compound # | Structure  | Source                         |
|------------|--|--------------------------------|
| 123        |    | WO #91/19715<br>pub. 26 Dec 91 |
| 124        |   | WO #91/19715<br>pub. 26 Dec 91 |
| 125        |  | WO #91/19715<br>pub. 26 Dec 91 |



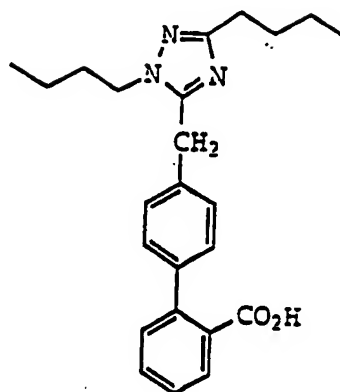
TABLE II: Angiotensin II Antagonists

Compound #

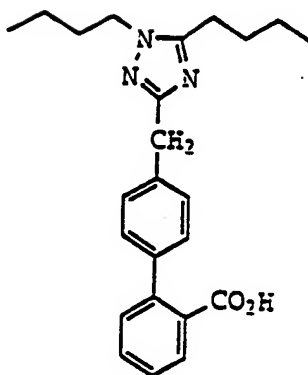
Structure

Source

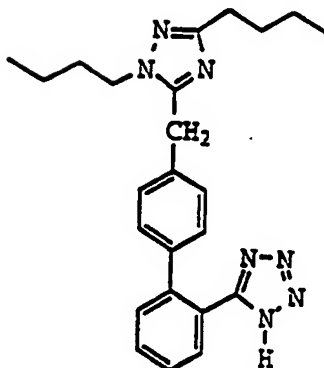
126

WO #92/05161  
pub. 2 Apr 92

127

WO #92/05161  
pub. 2 Apr 92

128

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pub. 2 Apr 92

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TABLE II: Angiotensin II Antagonists

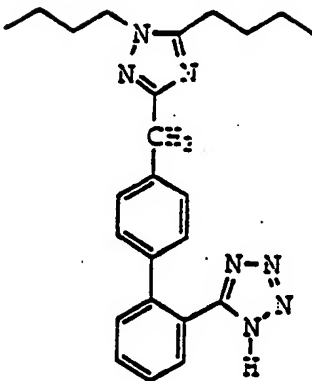
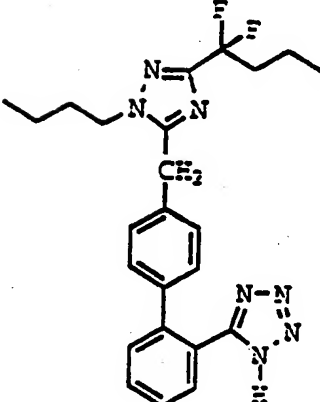
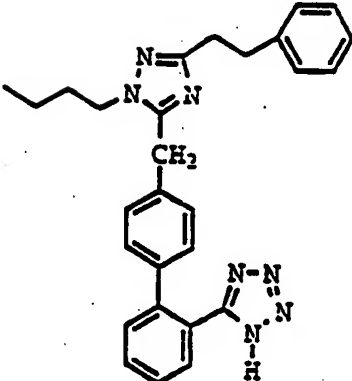
| Compound # | Structure   | Source                        |
|------------|---|-------------------------------|
| 129        |    | WO #92/05161<br>pub. 2 Apr 92 |
| 130        |   | WO #92/05161<br>pub. 2 Apr 92 |
| 131        |  | WO #92/05161<br>pub. 2 Apr 92 |

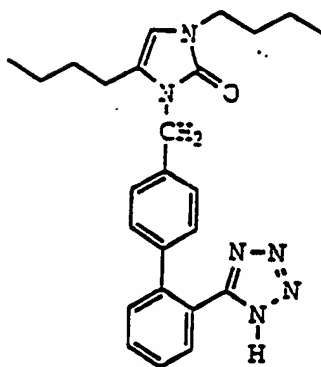
TABLE II: Angiotensin II Antagonists

Compound #

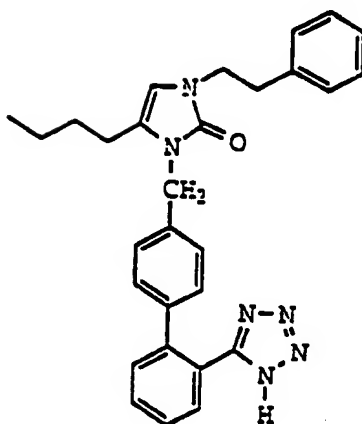
Structure

Source

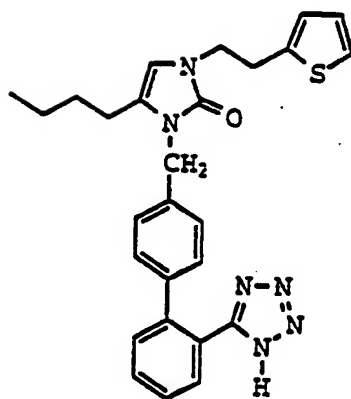
132

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pub. 14 May 92

133

WO #92/07834  
pub. 14 May 92

134

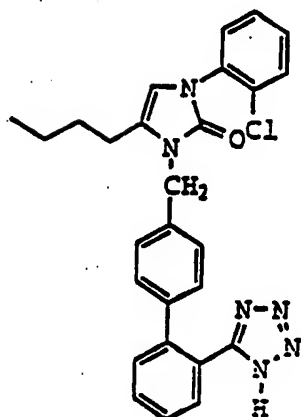
WO #92/07834  
pub. 14 May 92

70

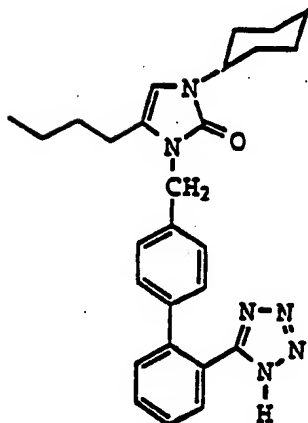
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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137

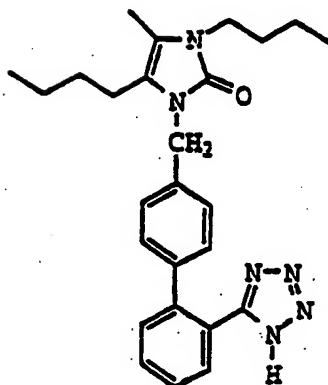
WO #92/07834  
pub. 14 May 92

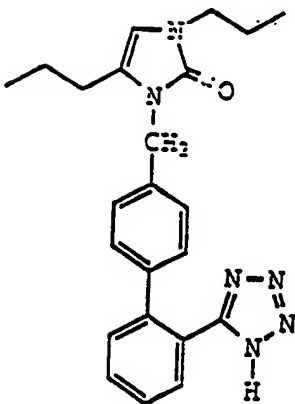
TABLE II: Angiotensin II Antagonists

Compound #

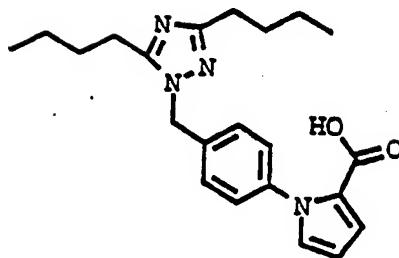
Structure

Source

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pub. 14 May 92

139

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pub. 9 Jul 92

140

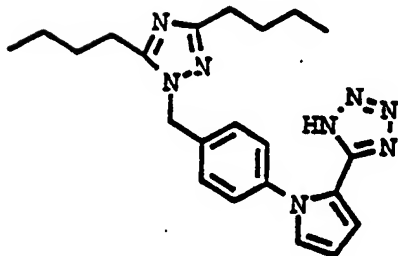
WO #92/11255  
pub. 9 Jul 92

TABLE II: Angiotensin II Antagonists

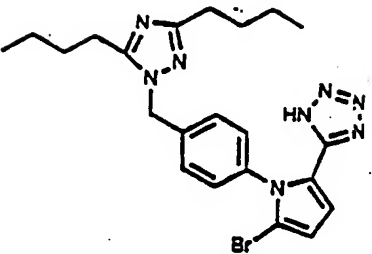
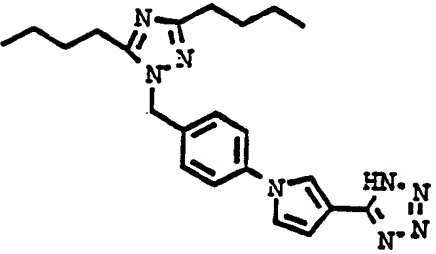
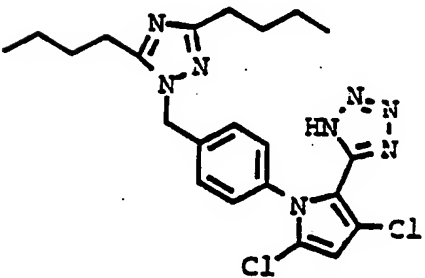
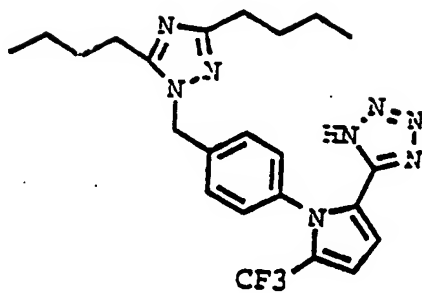
| Compound # | Structure  | Source                        |
|------------|--|-------------------------------|
| 141        |    | WO #92/11255<br>pub. 9 Jul 92 |
| 142        |   | WO #92/11255<br>pub. 9 Jul 92 |
| 143        |  | WO #92/11255<br>pub. 9 Jul 92 |

TABLE II: Angiotensin II Antagonists

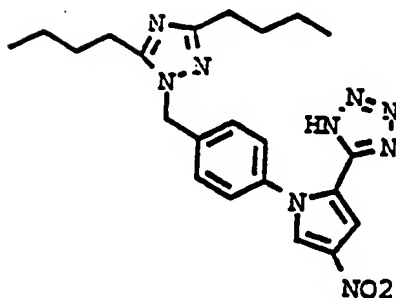
| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

144



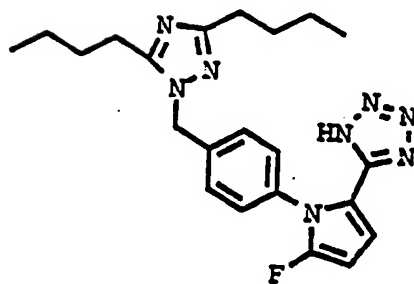
WO #92/11255  
pub. 9 Jul 92

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pub. 9 Jul 92

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pub. 9 Jul 92

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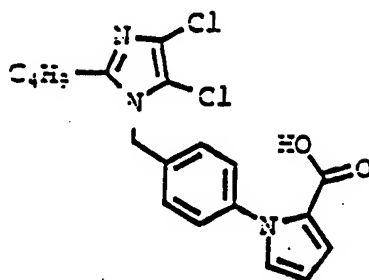
TABLE II: Angiotensin II Antagonists

Compound #

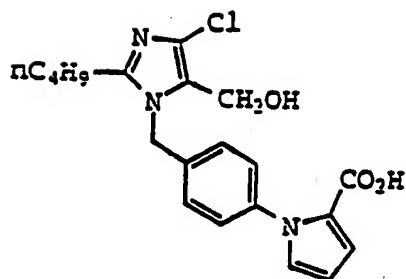
Structure

Source

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148

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pub. 17 Sep 92

149

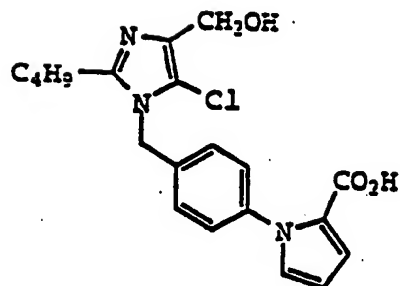
WO #92/15577  
pub. 17 Sep 92



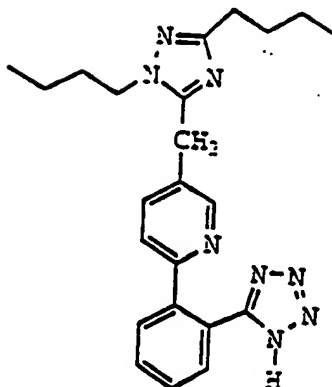
TABLE II: Angiotensin II Antagonists

Compound #

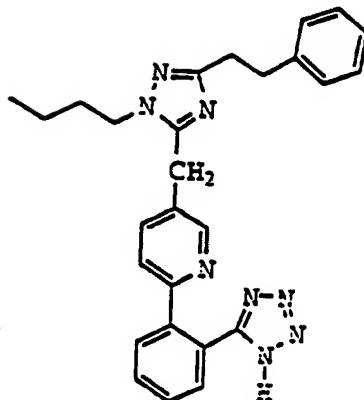
Structure

Source

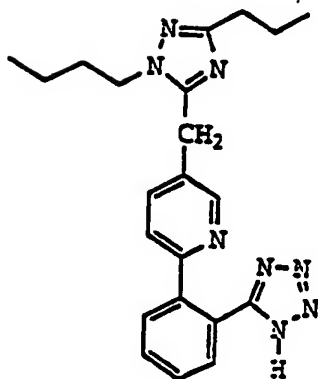
150

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151

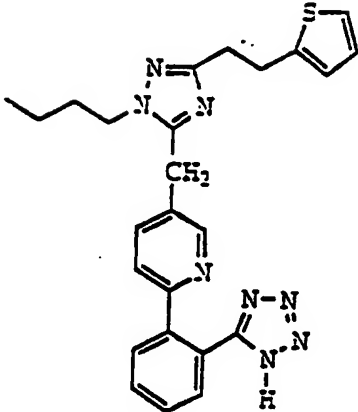
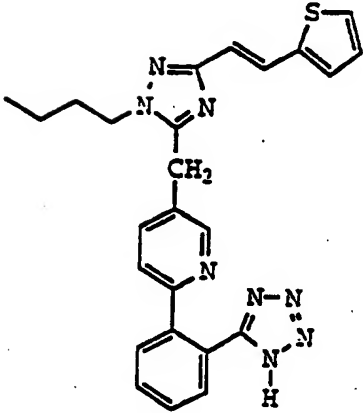
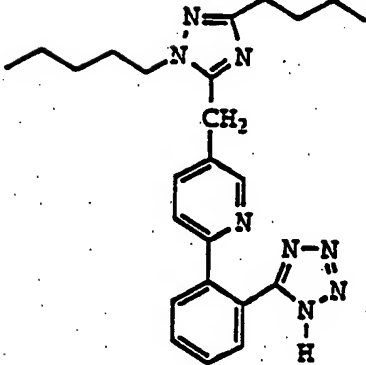
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pub. 1 Oct 92

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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                        |
|------------|---|-------------------------------|
| 153        |    | WO #92/16523<br>pub. 1 Oct 92 |
| 154        |   | WO #92/16523<br>pub. 1 Oct 92 |
| 155        |  | WO #92/16523<br>pub. 1 Oct 92 |

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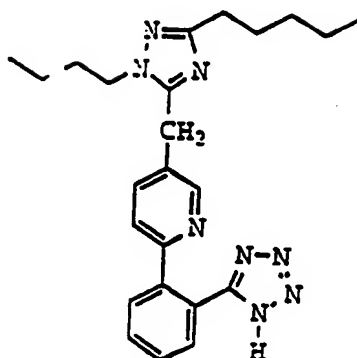
TABLE II: Angiotensin II Antagonists

Compound #

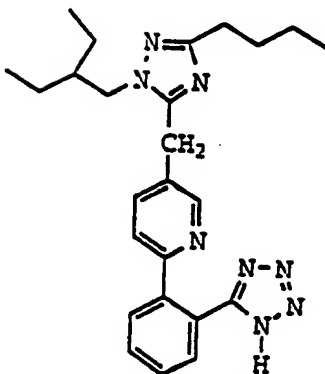
Structure

Source

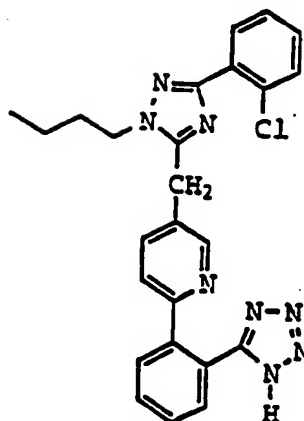
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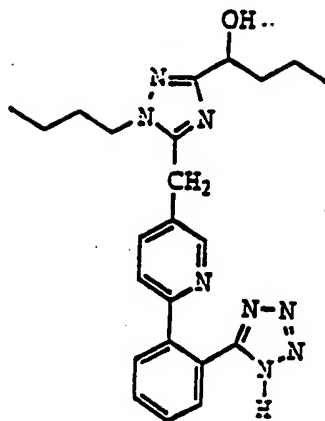
WO #92/16523  
pub. 1 Oct 92

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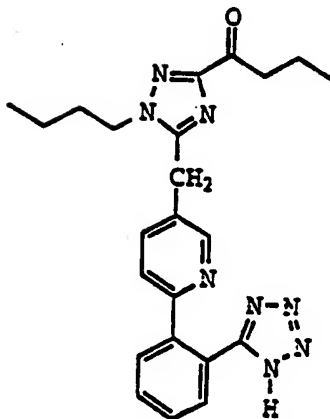
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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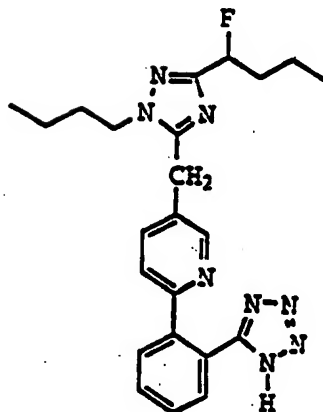
WO #92/16523  
pub. 1 Oct 92

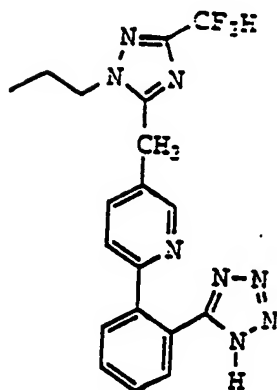
TABLE II: Angiotensin II Antagonists

Compound #

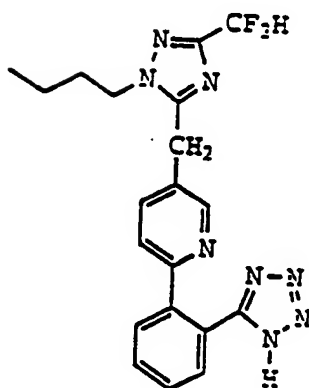
Structure

Source

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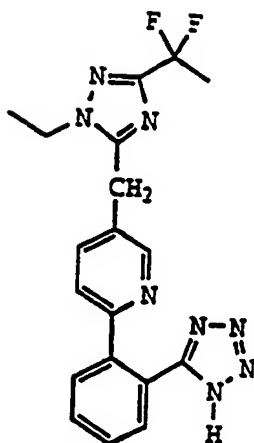
WO #92/16523  
pub. 1 Oct 92

TABLE II: Angiotensin II Antagonists

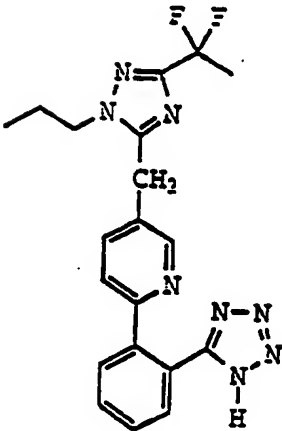
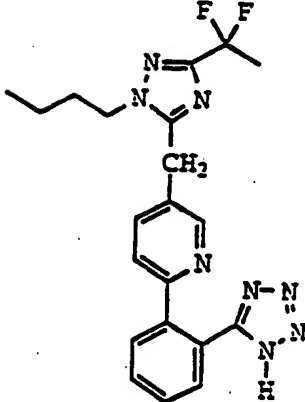
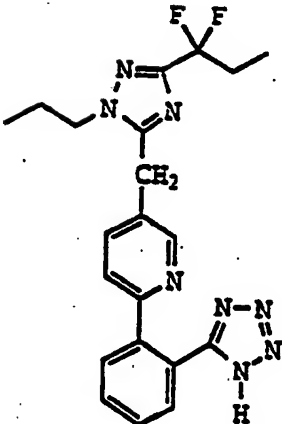
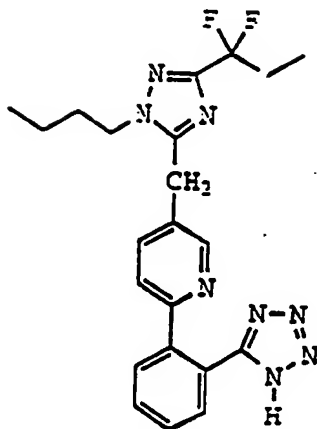
| Compound # | Structure   | Source                        |
|------------|---|-------------------------------|
| 165        |    | WO #92/16523<br>pub. 1 Oct 92 |
| 166        |   | WO #92/16523<br>pub. 1 Oct 92 |
| 167        |  | WO #92/16523<br>pub. 1 Oct 92 |

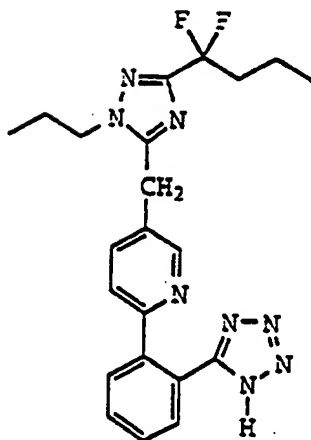
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

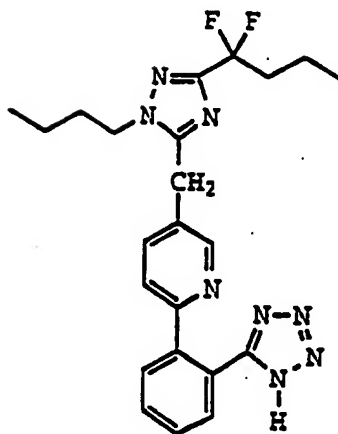
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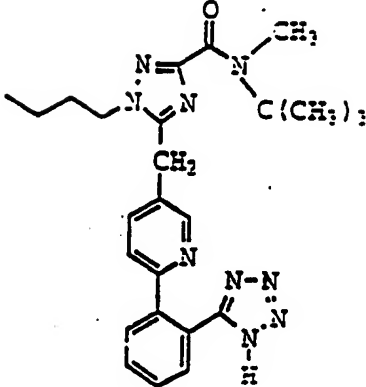
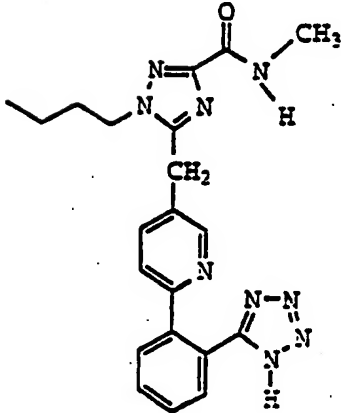
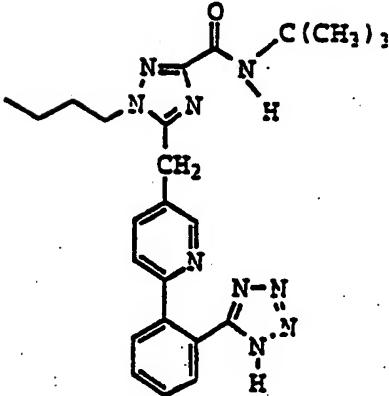
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                        |
|------------|--|-------------------------------|
| 171        |     | WO #92/16523<br>pub. 1 Oct 92 |
| 172        |    | WO #92/16523<br>pub. 1 Oct 92 |
| 173        |  | WO #92/16523<br>pub. 1 Oct 92 |



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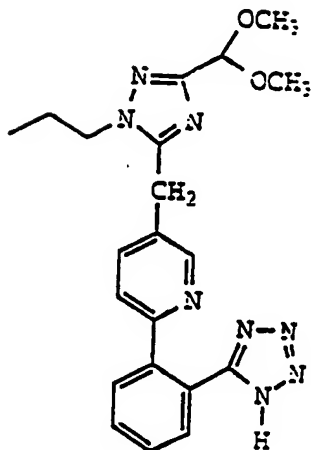
TABLE II: Angiotensin II Antagonists

Compound #

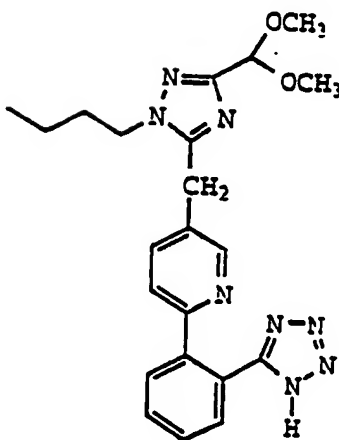
Structure

Source

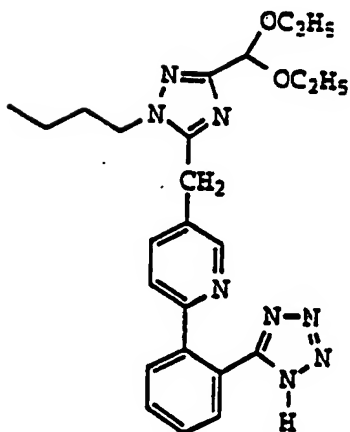
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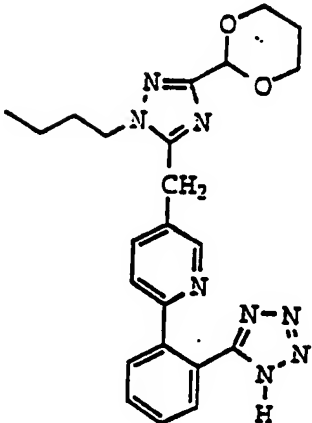
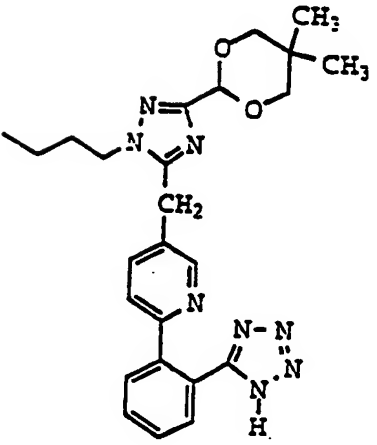
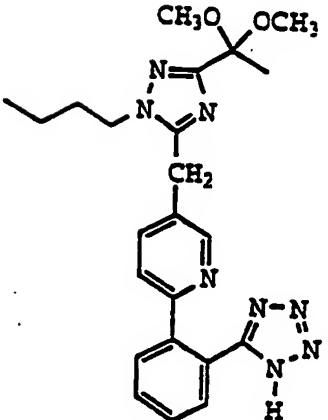
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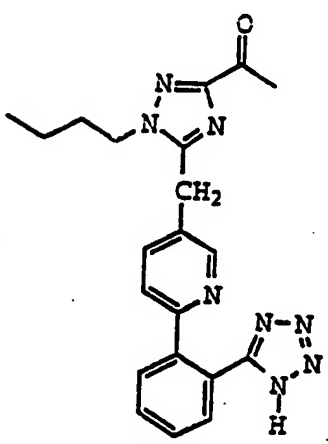
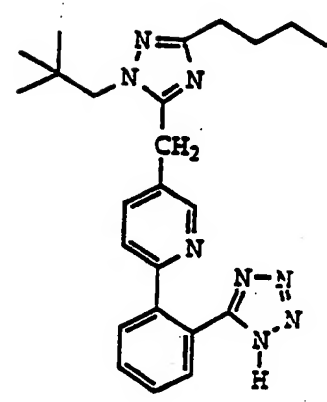
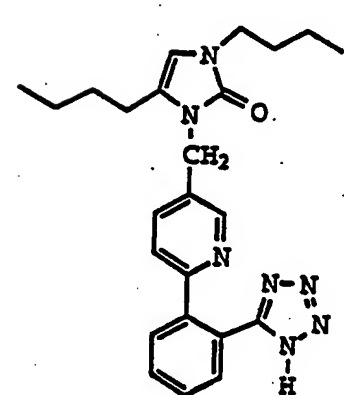
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                        |
|------------|---|-------------------------------|
| 180        |    | WO #92/16523<br>pub. 1 Oct 92 |
| 181        |  | WO #92/16523<br>pub. 1 Oct 92 |
| 182        |  | WO #92/16523<br>pub. 1 Oct 92 |

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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 183        |    | WO #92/16523<br>pub. 1 Oct 92  |
| 184        |   | WO #92/16523<br>pub. 1 Oct 92  |
| 185        |  | WO #92/17469<br>pub. 15 Oct 92 |

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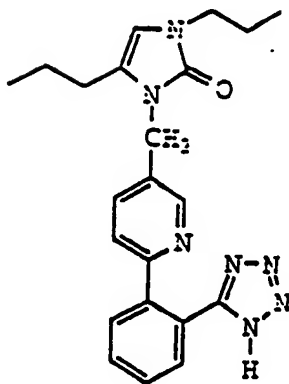
TABLE II: Angiotensin II Antagonists

Compound #

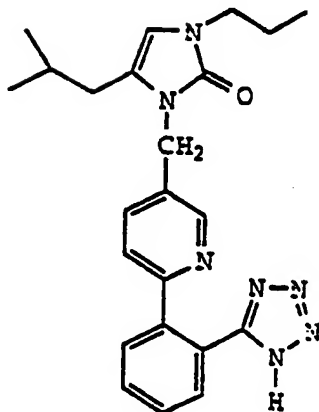
Structure

Source

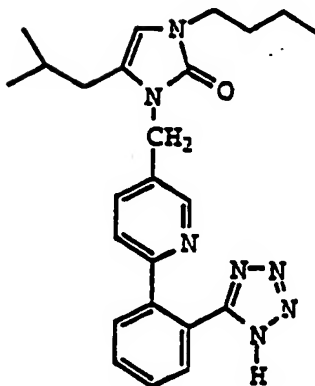
186

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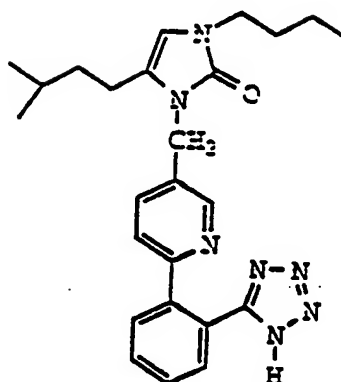
TABLE II: Angiotensin II Antagonists

Compound #

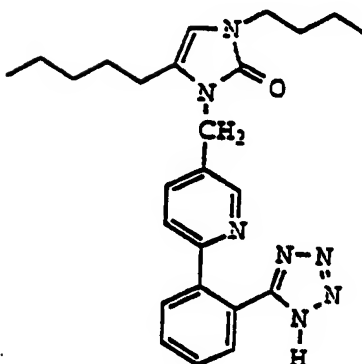
Structure

Source

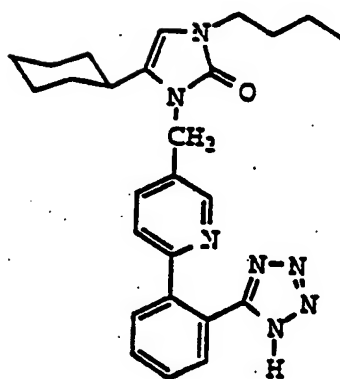
189

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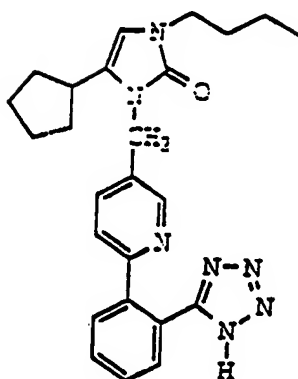
TABLE II: Angiotensin II Antagonists

Compound #

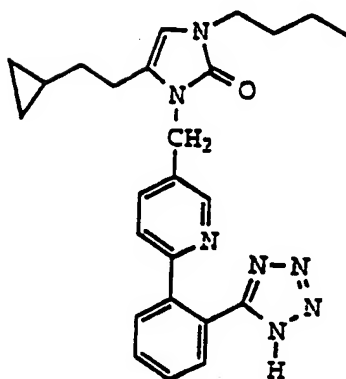
Structure

Source

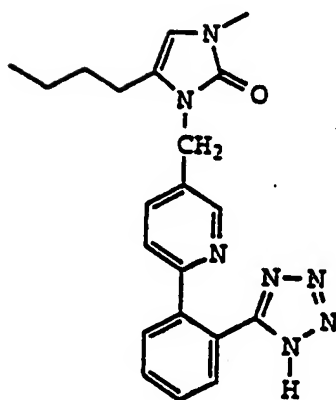
192

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pub. 15 Oct 92

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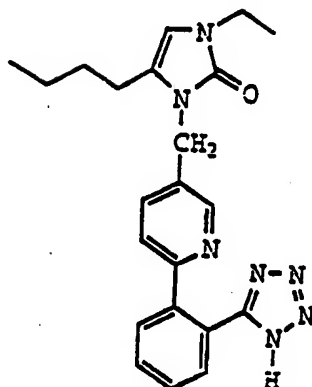
WO #92/17469  
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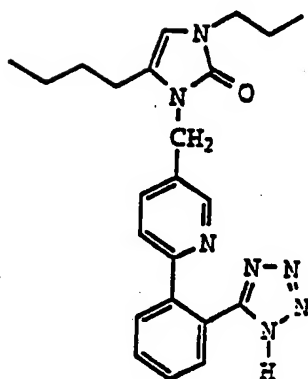
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

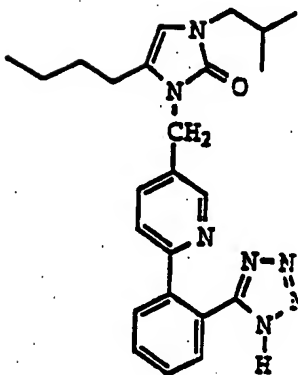
195

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197

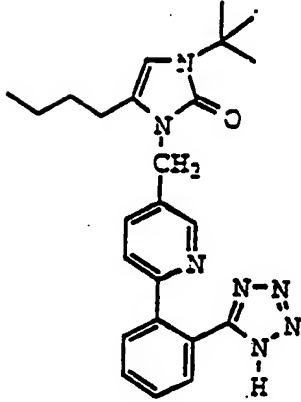
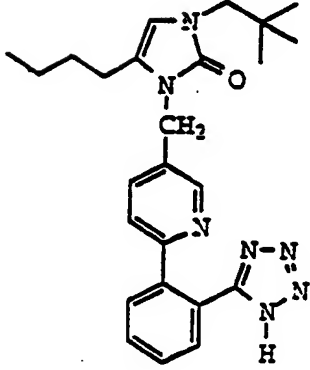
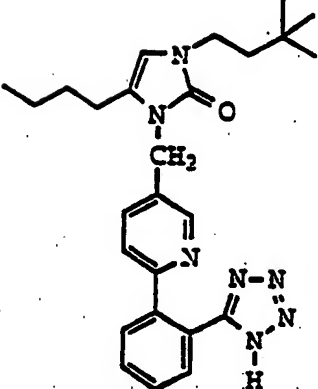
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 201        |    | WO #92/17469<br>pub. 15 Oct 92 |
| 202        |   | WO #92/17469<br>pub. 15 Oct 92 |
| 203        |  | WO #92/17469<br>pub. 15 Oct 92 |

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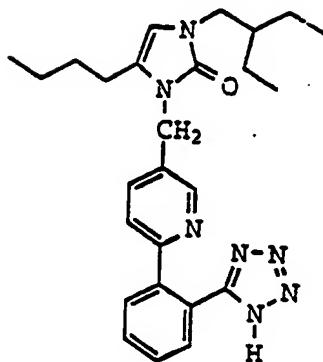
TABLE II: Angiotensin II Antagonists

Compound #

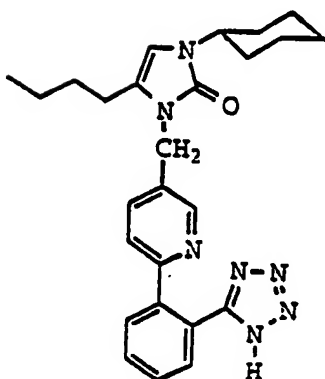
Structure

Source

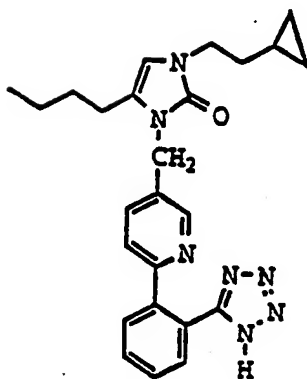
204

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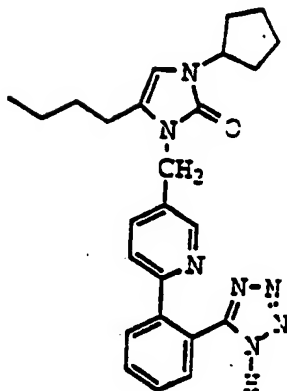
TABLE II: Angiotensin II Antagonists

Compound #

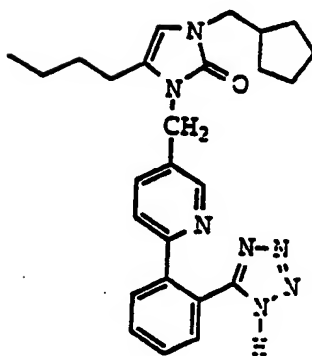
Structure

Source

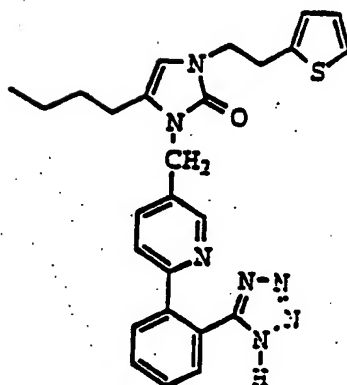
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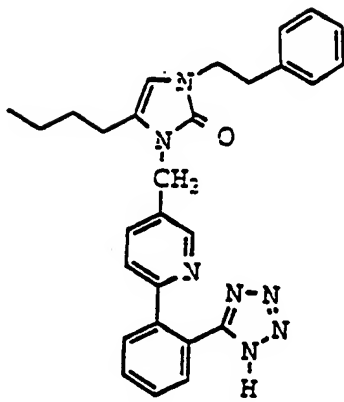
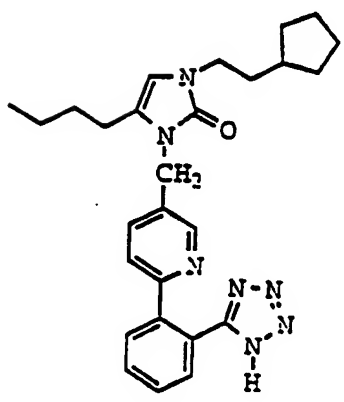
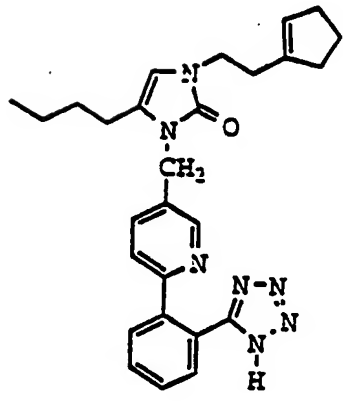
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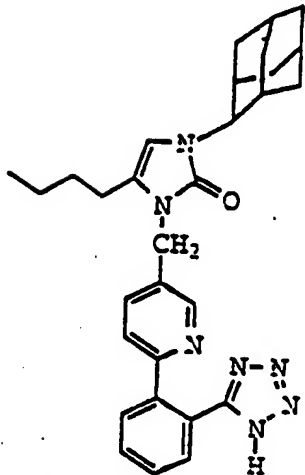
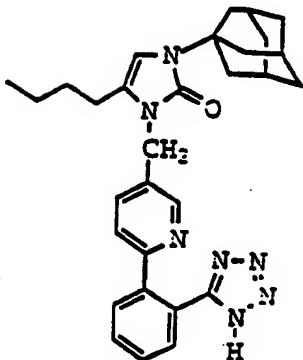
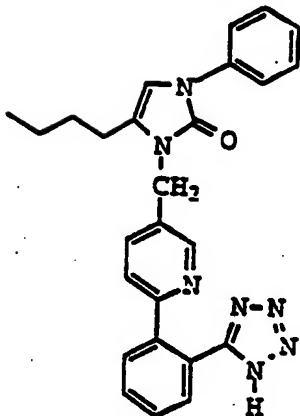
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 210        |    | WO #92/17469<br>pub. 15 Oct 92 |
| 211        |   | WO #92/17469<br>pub. 15 Oct 92 |
| 212        |  | WO #92/17469<br>pub. 15 Oct 92 |

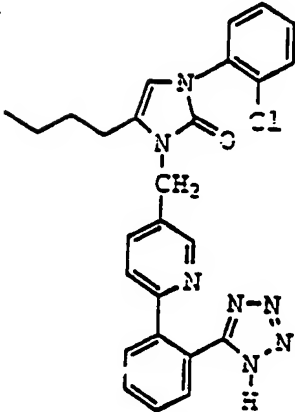
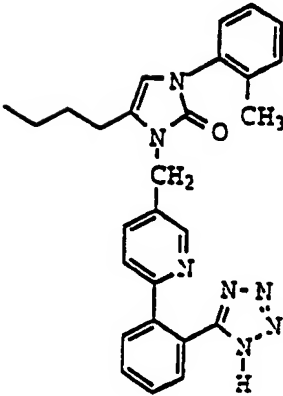
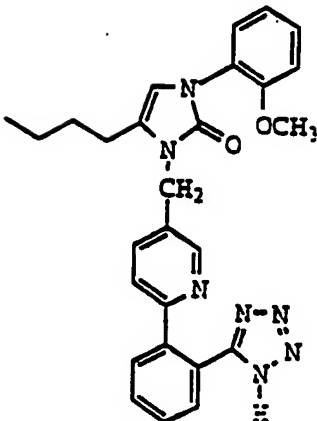
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 213        |    | WO #92/17469<br>pub. 15 Oct 92 |
| 214        |   | WO #92/17469<br>pub. 15 Oct 92 |
| 215        |  | WO #92/17469<br>pub. 15 Oct 92 |

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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 216        |    | WO #92/17469<br>pub. 15 Oct 92 |
| 217        |   | WO #92/17469<br>pub. 15 Oct 92 |
| 218        |  | WO #92/17469<br>pub. 15 Oct 92 |

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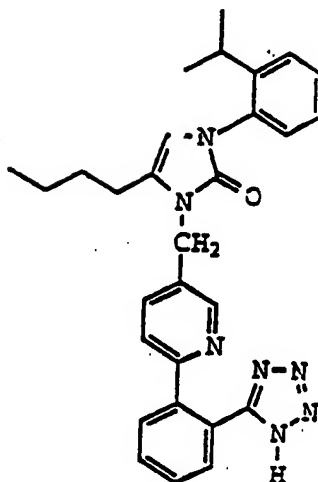
TABLE II: Angiotensin II Antagonists

Compound #

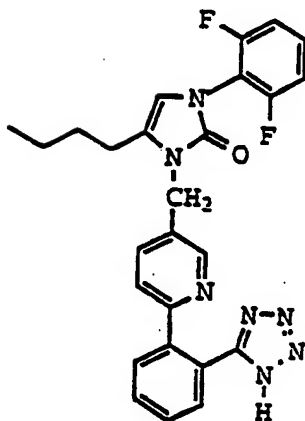
Structure

Source

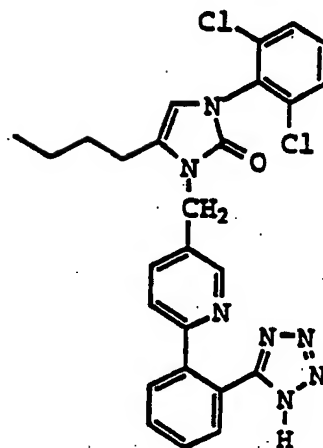
219

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220

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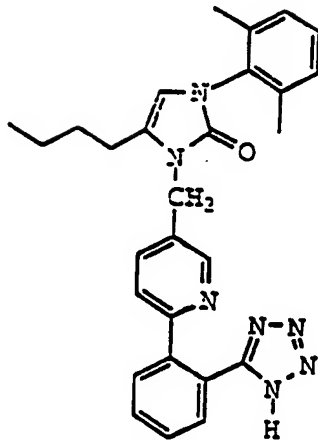
TABLE II: Angiotensin II Antagonists

Compound #

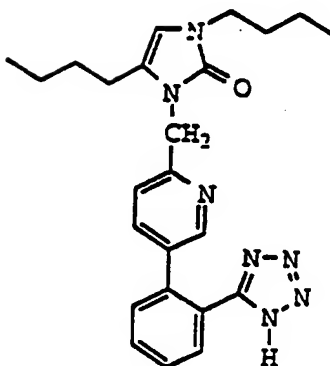
Structure

Source

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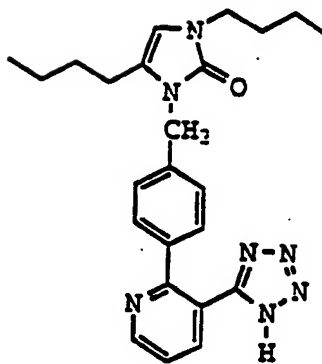
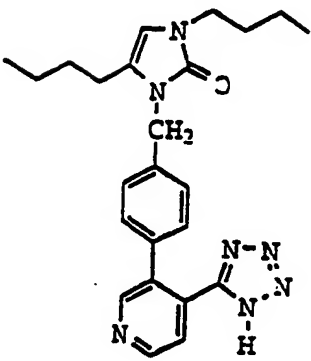
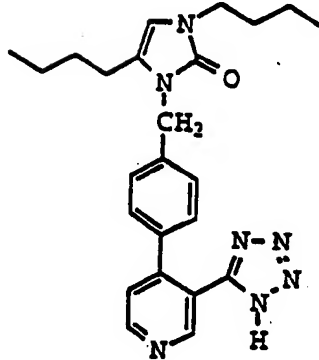
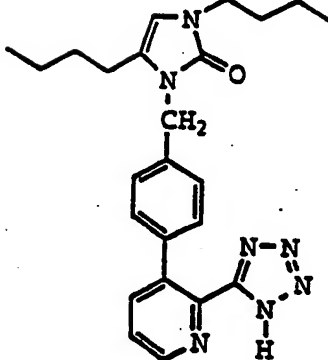
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pub. 15 Oct 92

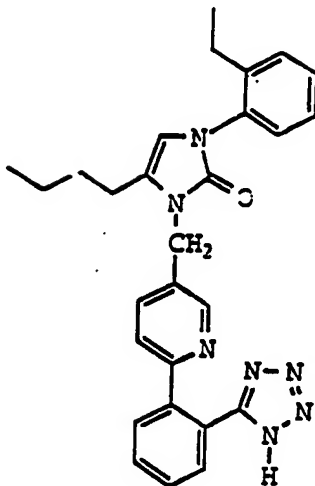
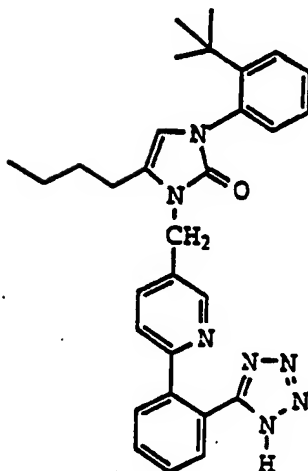
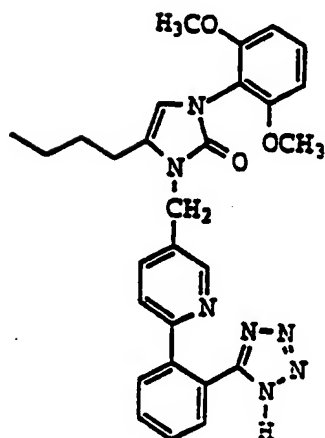
TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 225        |    | WO #92/17469<br>pub. 15 Oct 92 |
| 226        |   | WO #92/17469<br>pub. 15 Oct 92 |
| 227        |  | WO #92/17469<br>pub. 15 Oct 92 |

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**TABLE II:** Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

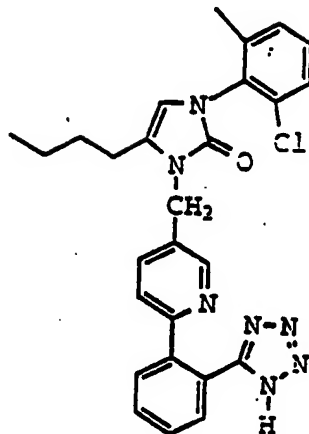
228229230

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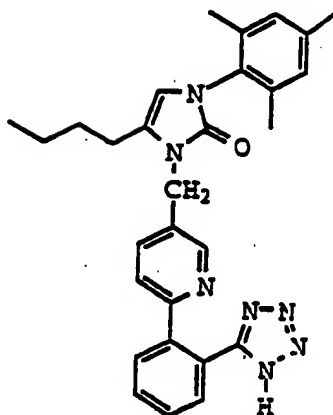
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

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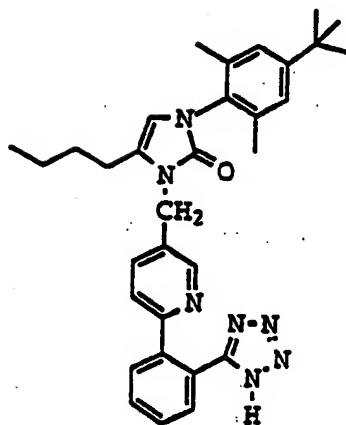
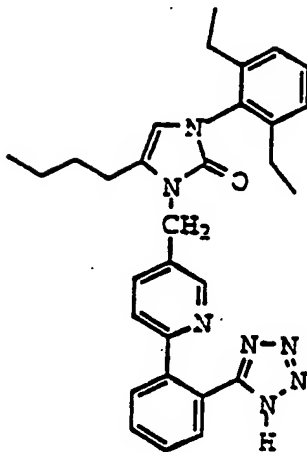


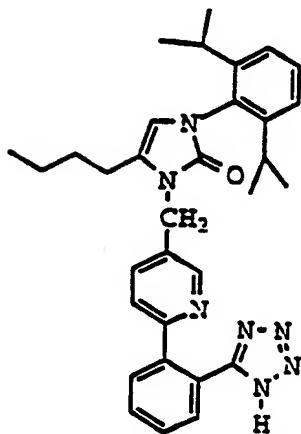
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

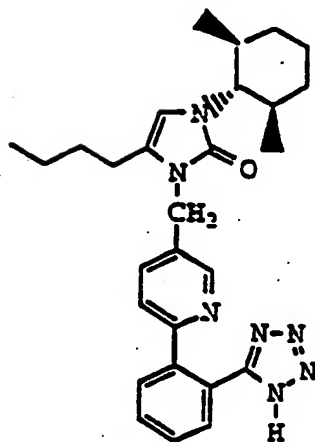
234



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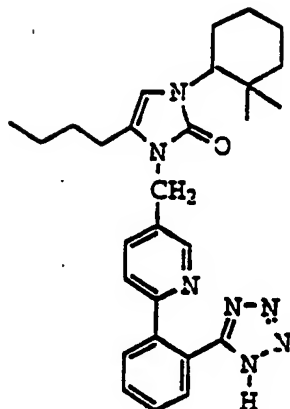


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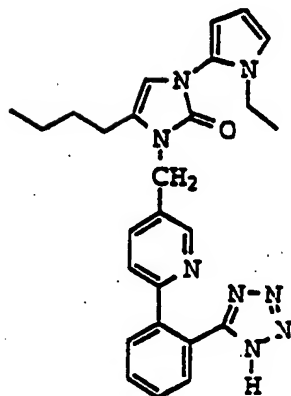
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

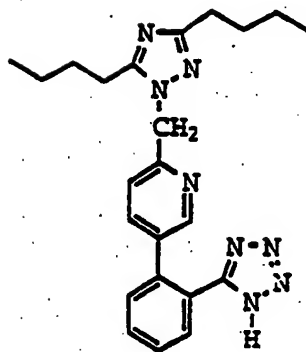
237



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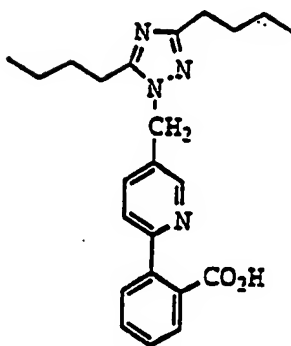
TABLE II: Angiotensin II Antagonists

Compound #

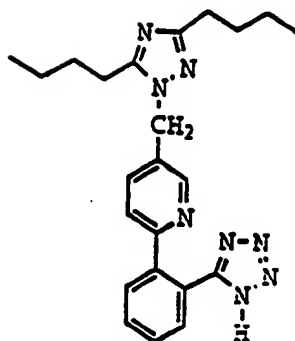
Structure

Source

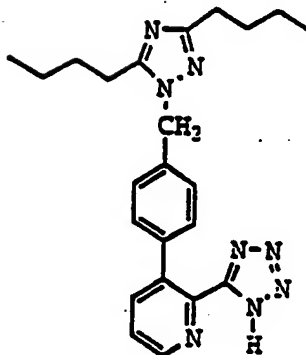
240

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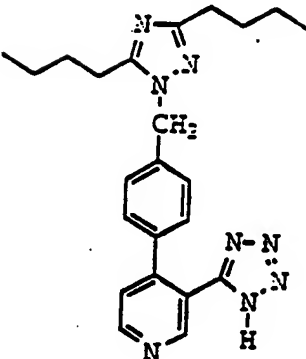
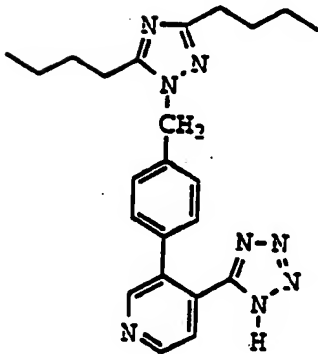
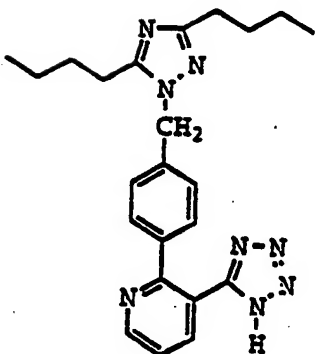
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 243        |    | WO #92/18092<br>pub. 29 Oct 92 |
| 244        |   | WO #92/18092<br>pub. 29 Oct 92 |
| 245        |  | WO #92/18092<br>pub. 29 Oct 92 |



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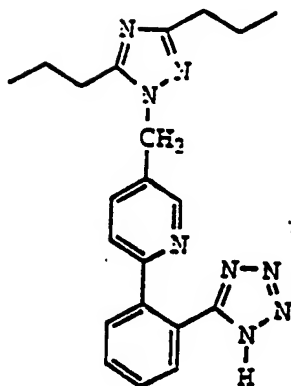
TABLE II: Angiotensin II Antagonists

Compound #

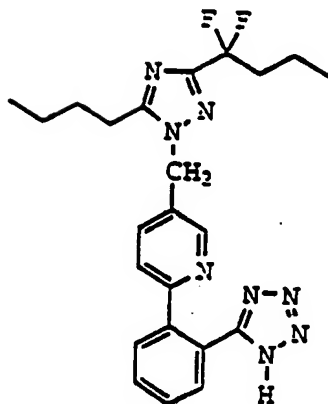
Structure

Source

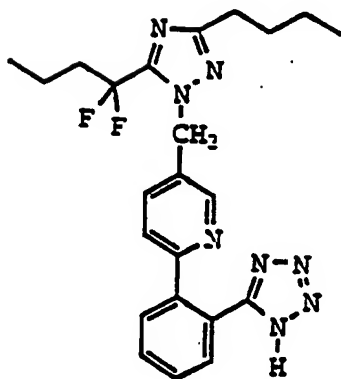
246

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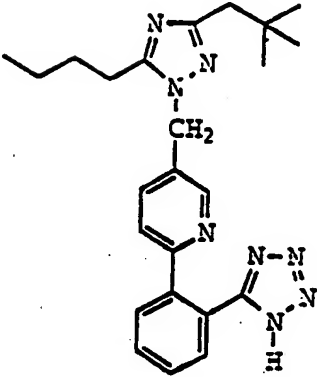
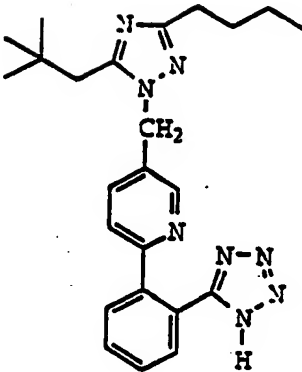
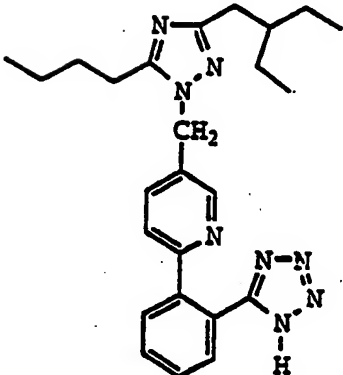
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 249        |    | WO #92/18092<br>pub. 29 Oct 92 |
| 250        |   | WO #92/18092<br>pub. 29 Oct 92 |
| 251        |  | WO #92/18092<br>pub. 29 Oct 92 |

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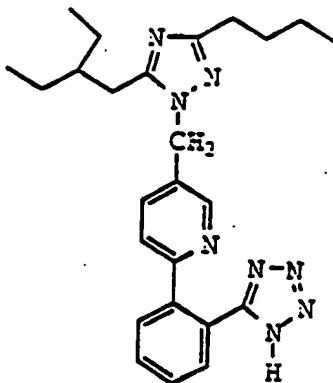
TABLE II: Angiotensin II Antagonists

Compound #

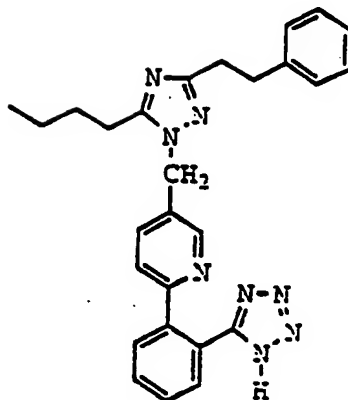
Structure

Source

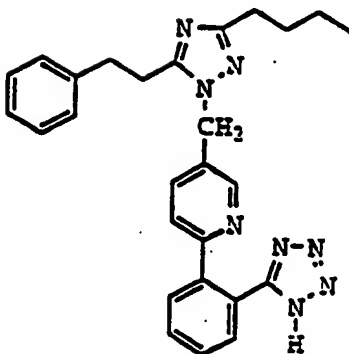
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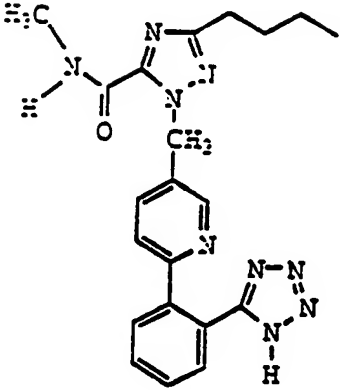
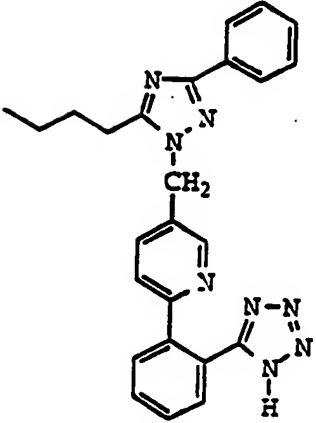
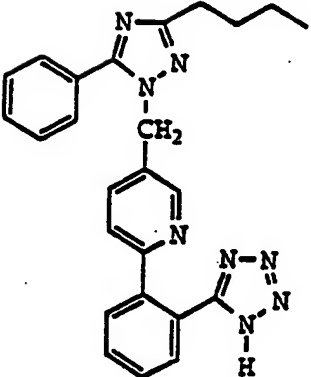
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 255        | <br><chem>CCCC1=NC(=C(C(=N1)C(=O)N(C)C)C2=CC=CC=C2C3=CC=CC=C3C4=NN=CN4)C5=CC=CC=C5C6=CC=CC=C6C7=NN=CN7</chem> | WO #92/18092<br>pub. 29 Oct 92 |
| 256        | <br><chem>CCCC1=NC(=C(C(=N1)C(=O)N(C)C)C2=CC=CC=C2C3=CC=CC=C3C4=NN=CN4)C5=CC=CC=C5C6=CC=CC=C6C7=NN=CN7</chem> | WO #92/18092<br>pub. 29 Oct 92 |
| 257        | <br><chem>CCCC1=NC(=C(C(=N1)C(=O)N(C)C)C2=CC=CC=C2C3=CC=CC=C3C4=NN=CN4)C5=CC=CC=C5C6=CC=CC=C6C7=NN=CN7</chem> | WO #92/18092<br>pub. 29 Oct 92 |

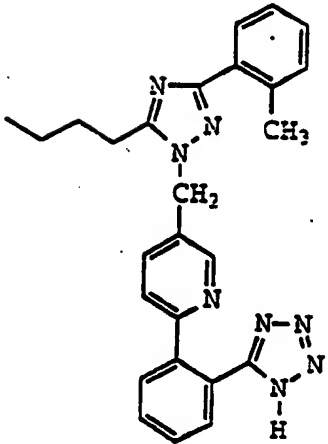
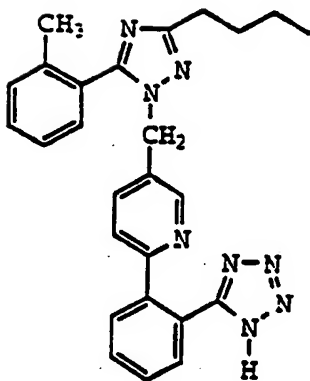
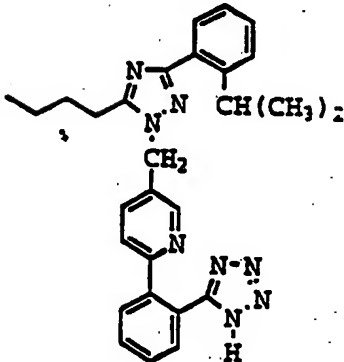
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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 258        |    | WO #92/18092<br>pub. 29 Oct 92 |
| 259        |   | WO #92/18092<br>pub. 29 Oct 92 |
| 260        |  | WO #92/18092<br>pub. 29 Oct 92 |

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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 261        |    | WO #92/18092<br>pub. 29 Oct 92 |
| 262        |   | WO #92/18092<br>pub. 29 Oct 92 |
| 263        |  | WO #92/18092<br>pub. 29 Oct 92 |

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TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 264        | <br><chem>CCCC1=CN(C2=CC=CC=C2C(=N1)CC3=CC=CC=C3C(=N4C=CC=CC=C4C5=CC=CC=C5C(=N6C=CC=CC=C6C(=N7C=CC=CC=C7C(=N8C=CC=CC=C8)N)N)N)N3</chem> | WO #92/18092<br>pub. 29 Oct 92 |
| 265        | <br><chem>CCCC1=CN(C2=CC=CC=C2C(=N1)CC3=CC=CC=C3C(=N4C=CC=CC=C4C5=CC=CC=C5C(=N6C=CC=CC=C6C(=N7C=CC=CC=C7C(=N8C=CC=CC=C8)N)N)N)N3</chem> | WO #92/18092<br>pub. 29 Oct 92 |
| 266        | <br><chem>CCCC1=CN(C2=CC=CC=C2C(=N1)CC3=CC=CC=C3C(=N4C=CC=CC=C4C5=CC=CC=C5C(=N6C=CC=CC=C6C(=N7C=CC=CC=C7C(=N8C=CC=CC=C8)N)N)N)N3</chem> | WO #92/18092<br>pub. 29 Oct 92 |

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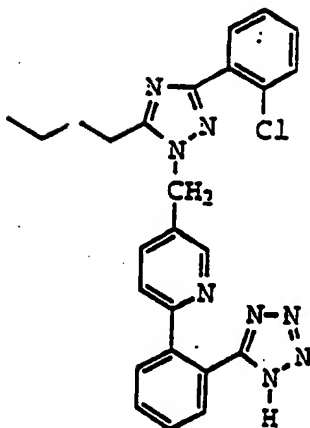
TABLE II: Angiotensin II Antagonists

Compound #

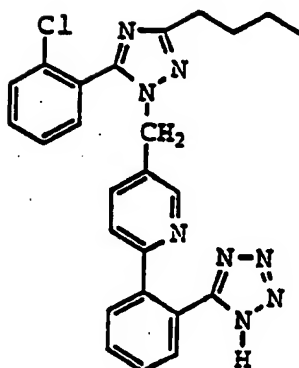
Structure

Source

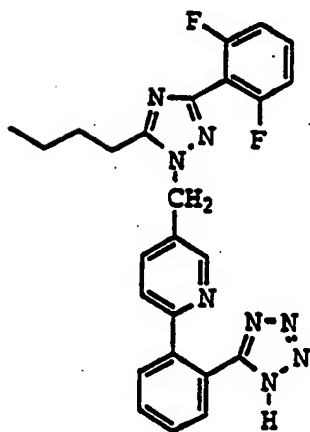
267

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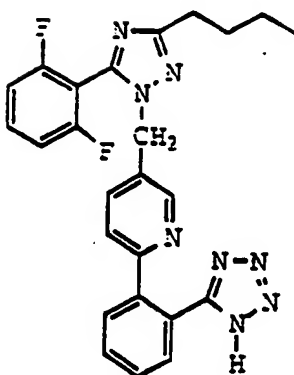
TABLE II: Angiotensin II Antagonists

Compound #

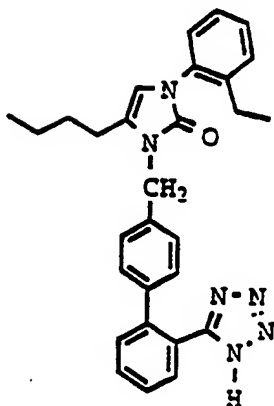
Structure

Source

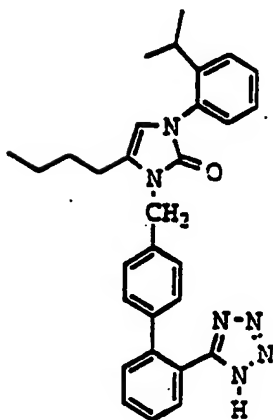
270

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filed 8 Mar 94

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PCT/US94/02156  
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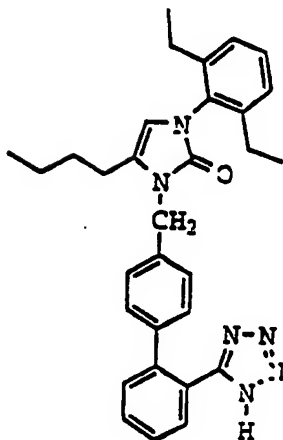
TABLE II: Angiotensin II Antagonists

Compound #

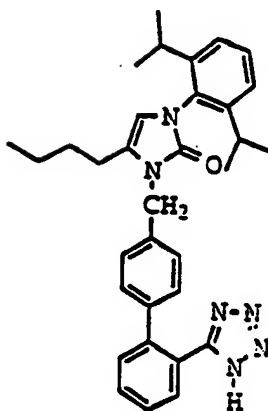
Structure

Source

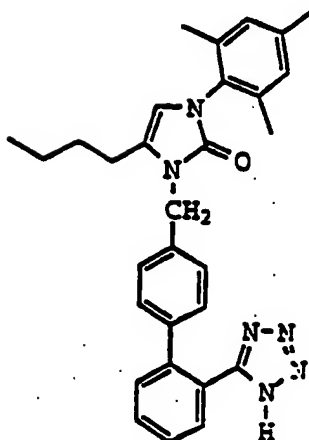
276

PCT/US94/02156  
filed 8 Mar 94

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PCT/US94/02156  
filed 8 Mar 94

278

PCT/US94/02156  
filed 8 Mar 94

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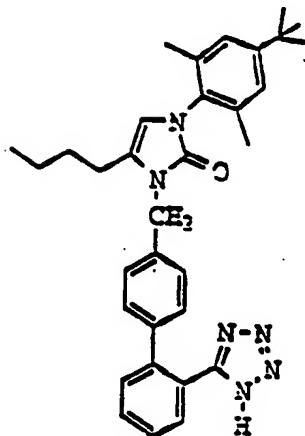
TABLE II: Angiotensin II Antagonists

Compound #

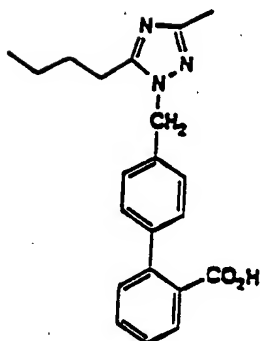
Structure

Source

279

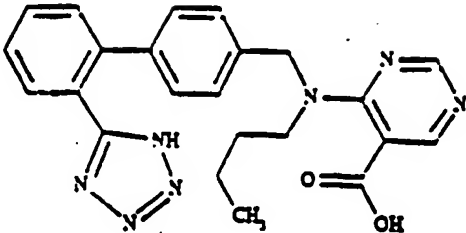
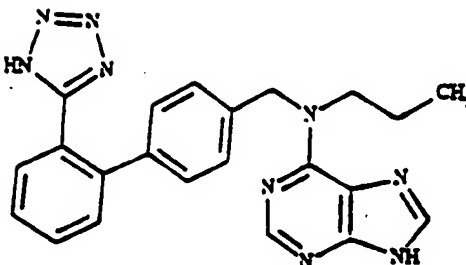
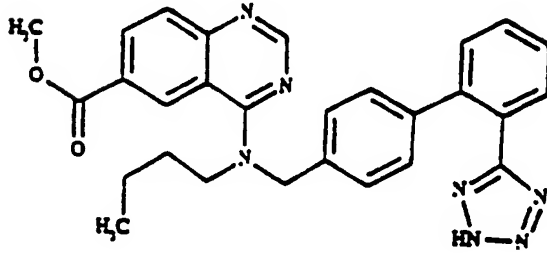
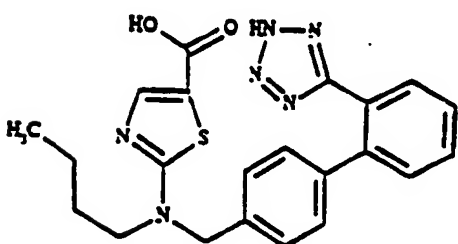
PCT/US94/02156  
filed 8 Mar. 94

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pub. 14 Nov 91

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TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                         |
|------------|--|--------------------------------|
| 281        |    | EP #475,206<br>pub. 18 Mar 92  |
| 282        |    | WO #93/18035<br>pub. 16 Sep 93 |
| 283        |  | WO #93/17628<br>pub. 16 Sep 93 |
| 284        |   | WO #93/17681<br>pub. 16 Sep 93 |

120

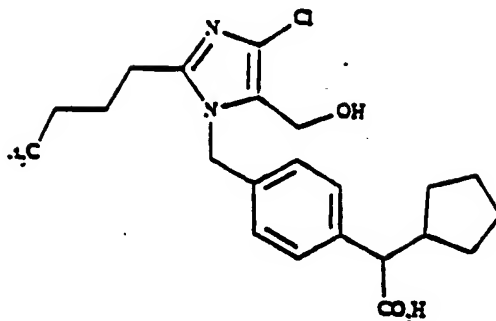
TABLE II: Angiotensin II Antagonists

Compound #

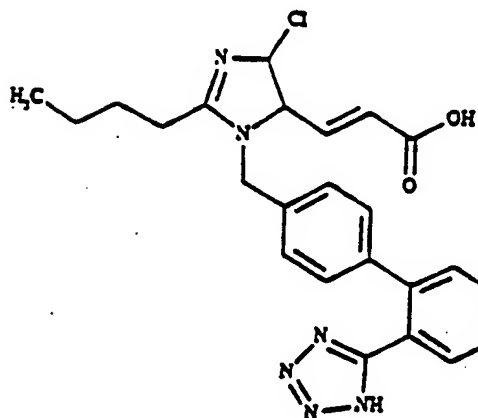
Structure

Source

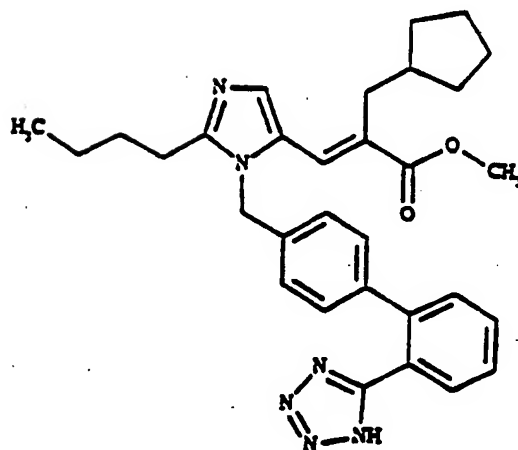
285

EP #513,533  
pub. 19 Nov 92

286

EP #535,463  
pub. 07 Apr 93

287

EP #535,465  
pub. 07 Apr 93

121

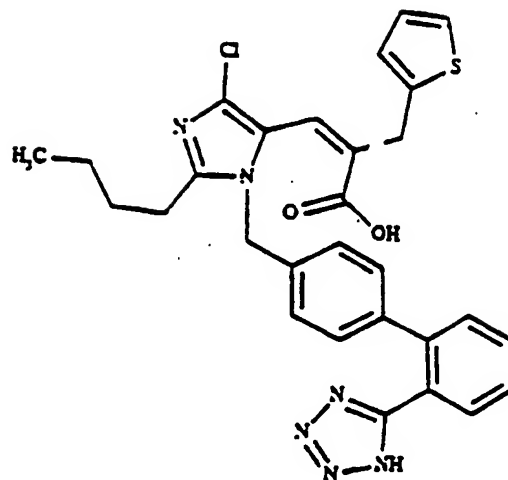
TABLE II: Angiotensin II Antagonists

Compound #

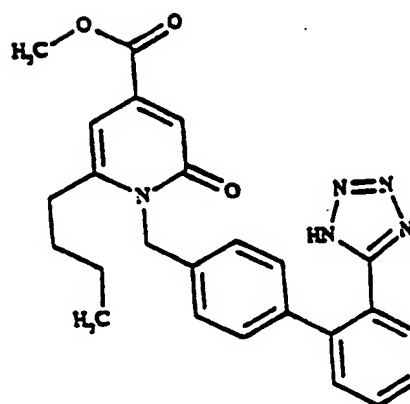
Structure

Source

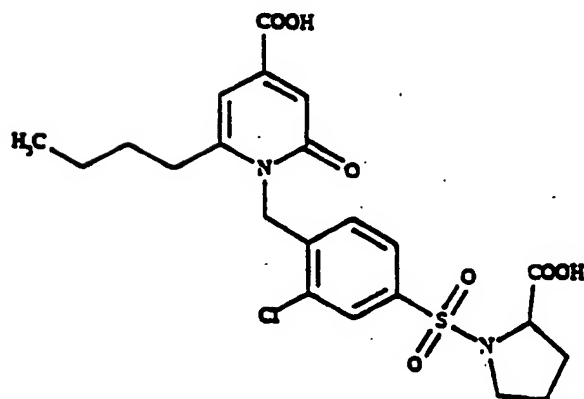
288

EP #539,713  
pub. 05 May 93

289

EP #542,059  
pub. 19 May 93

290

EP #05 557,843  
pub. 01 Sep 93

122

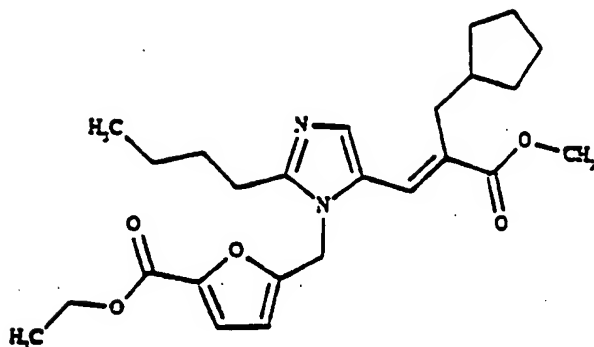
TABLE II: Angiotensin II Antagonists

Compound #

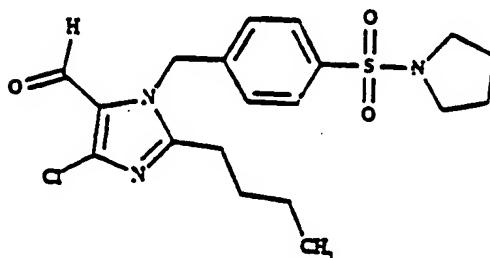
Structure

Source

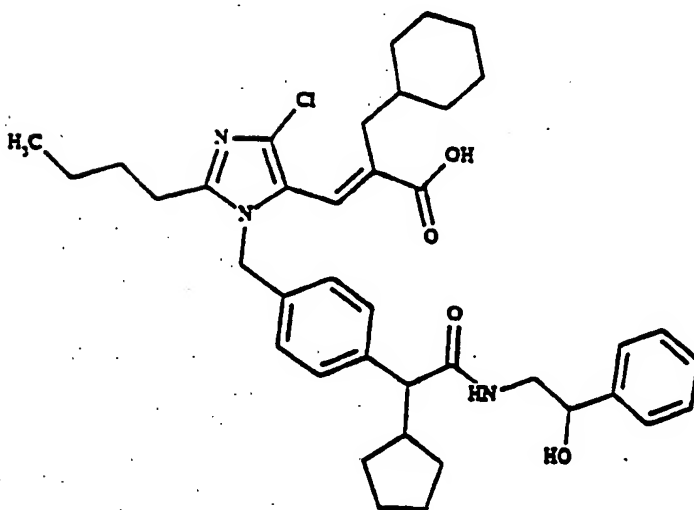
291

EP #563,705  
pub. 06 Oct 93

292

EP #562,261  
pub. 29 Sep 93

293

EP #05 557,843  
pub. 15 Sep 93



123

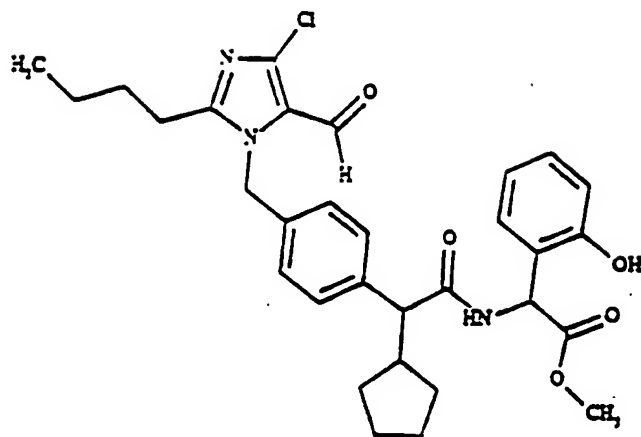
TABLE II: Angiotensin II Antagonists

Compound #

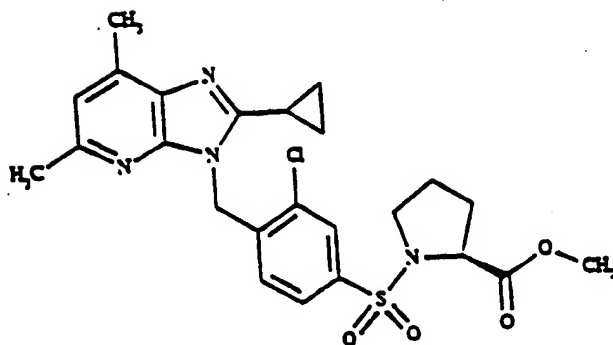
Structure

Source

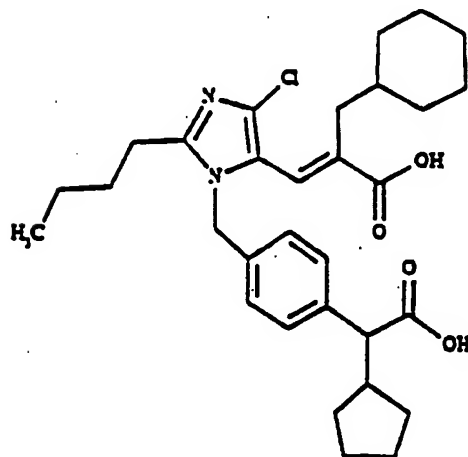
294

EP #560,163  
pub. 15 Sep 93

295

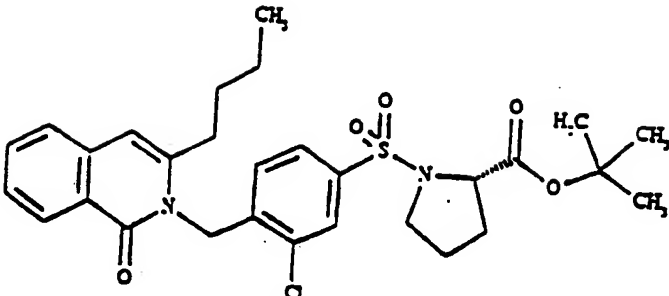
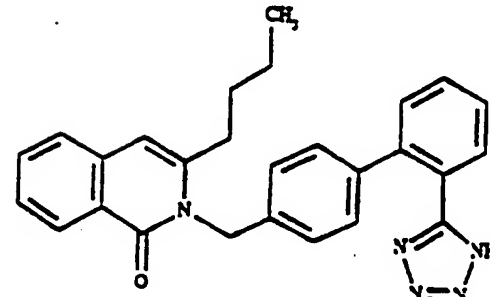
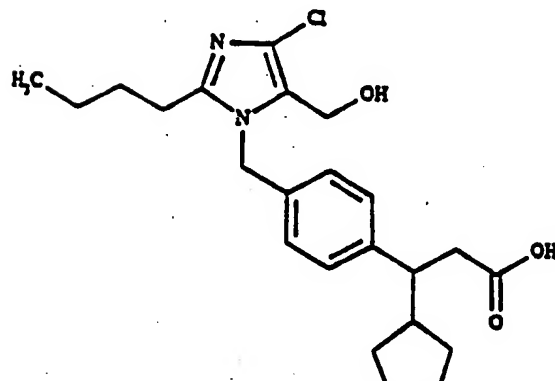
EP #564, 788  
pub. 13 Oct 93

296

EP #565,986  
pub. 20 Oct 93

124

TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                          |
|------------|--|---------------------------------|
| 297        |    | EP #0,569,795<br>pub. 18 Nov 93 |
| 298        |    | EP #0,569,794<br>pub. 18 Nov 93 |
| 299        |  | EP #0,578,002<br>pub. 12 Jan 94 |

125

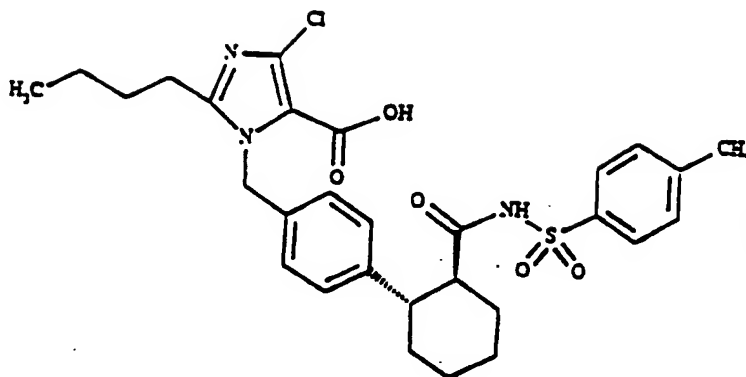
TABLE II: Angiotensin II Antagonists

Compound #

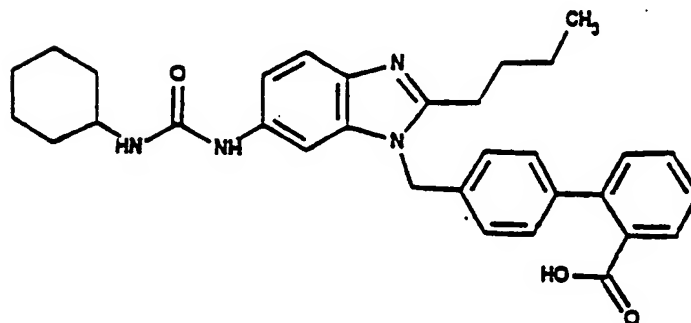
Structure

Source

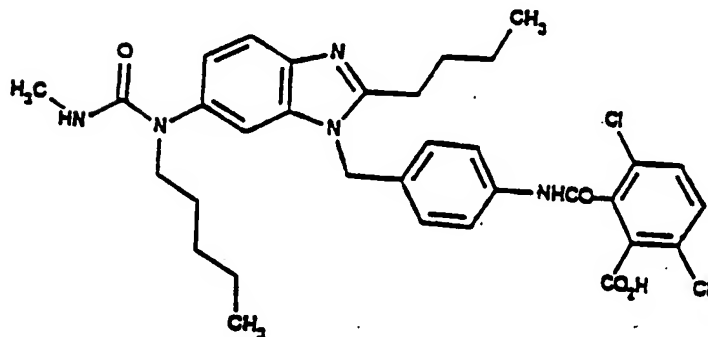
300

EP #581,003  
pub. 02 Feb 94

301

EP #392,317  
pub. 17 Oct 90

302

EP #392,317  
pub. 17 Oct 90

126

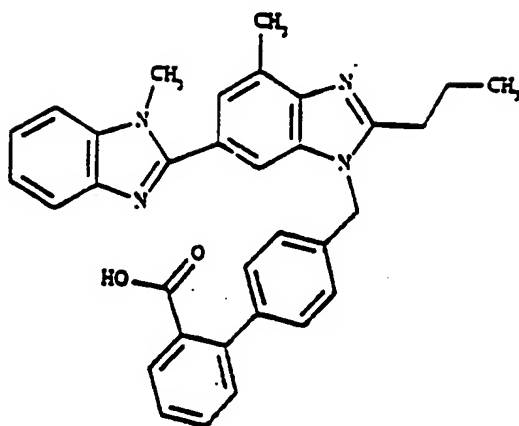
TABLE II: Angiotensin II Antagonists

Compound #

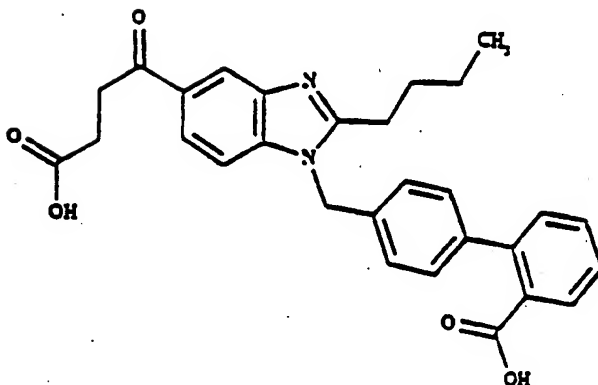
Structure

Source

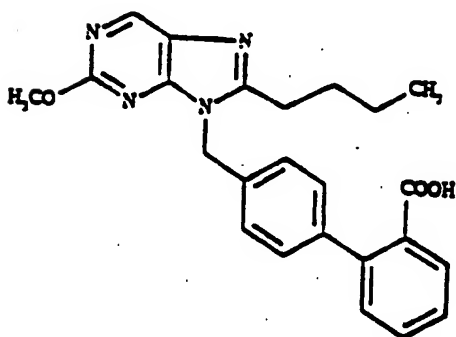
303

EP #502,314  
pub. 09 Sep 92

304

EP #468,740  
pub. 29 Jan 92

305

EP #470,543  
pub. 12 Feb 92

127

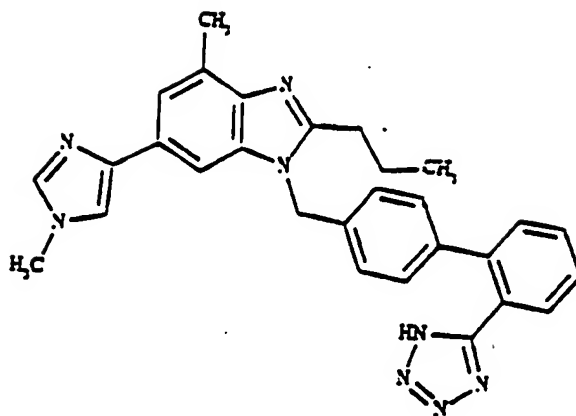
TABLE II: Angiotensin II Antagonists

Compound #

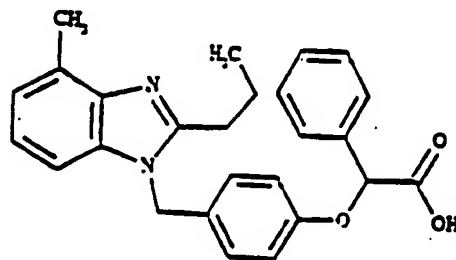
Structure

Source

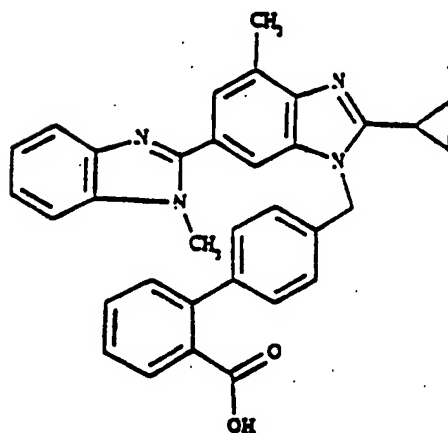
306

EP #502,314  
pub. 09 Sep 92

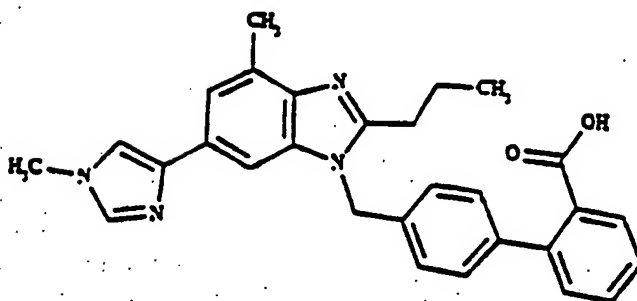
307

EP #529,253  
pub. 03 Mar 93

308

EP #543,263  
pub. 26 May 93

309

EP #552,765  
pub. 28 Jul 93

128

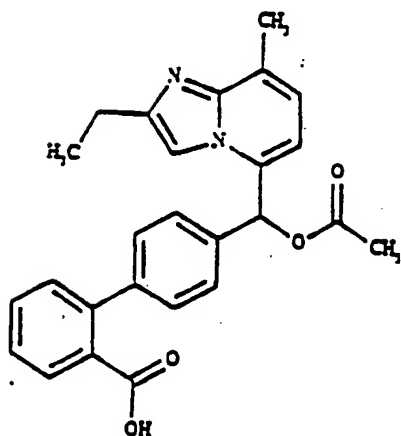
TABLE II: Angiotensin II Antagonists

Compound #

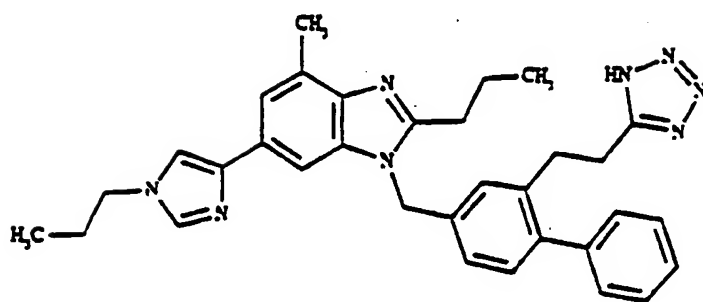
Structure

Source

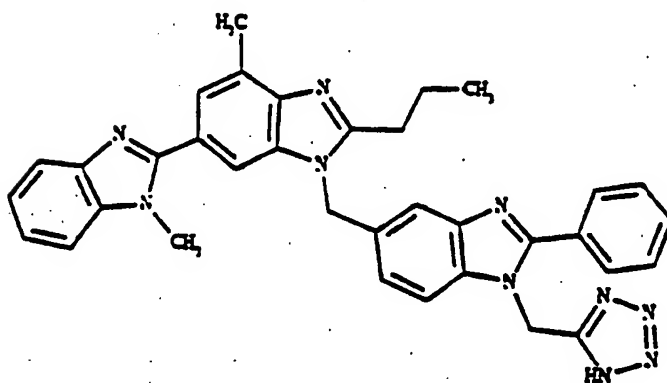
310

EP #555,825  
pub. 18 Aug 93

311

EP #556,789  
pub. 25 Aug 93

312

EP #560,330  
pub. 15 Sep 93

129

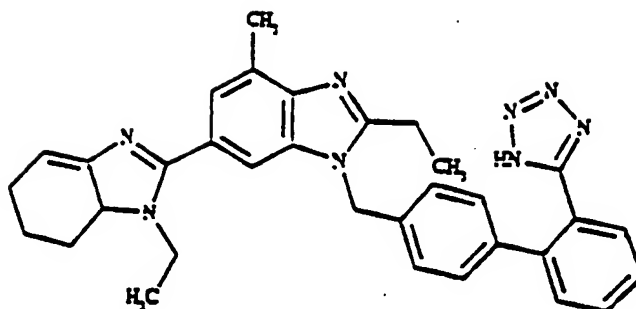
TABLE II: Angiotensin II Antagonists

Compound #

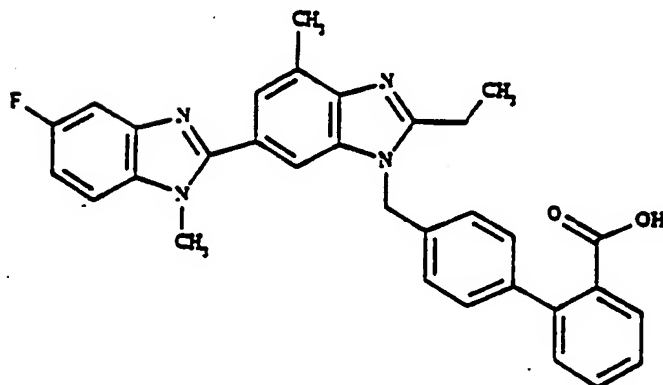
Structure

Source

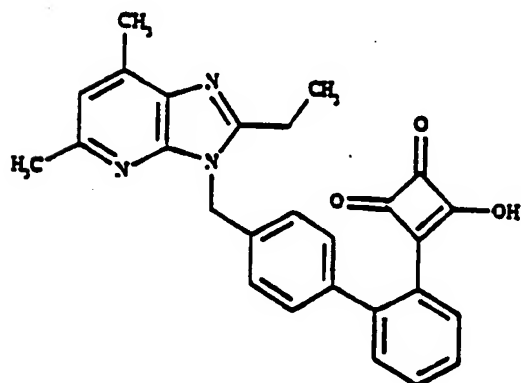
313

EP #566,020  
pub. 20 Oct 93

314

EP #581,166  
pub. 02 Feb 94

315

WO #94/01436  
pub. 20 Jan 94

130

**TABLE II:** Angiotensin II Antagonists

| Compound # | Structure | Source                            |
|------------|-----------|-----------------------------------|
| 316        |           | EP #253,310<br>pub. 20 Jan 88     |
| 317        |           | EP #324,377<br>pub. 19 Jul 89     |
| 318        |           | US #5,043,349<br>issued 27 Aug 91 |
| 319        |           | WO #91/00281<br>pub. 10 Jan 91    |



131

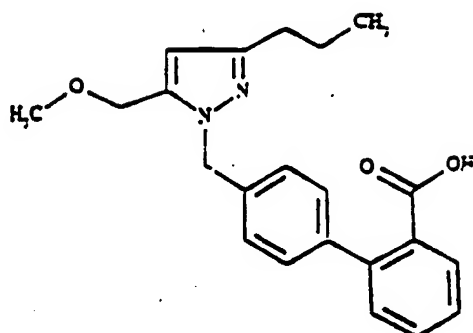
TABLE II: Angiotensin II Antagonists

Compound #

Structure

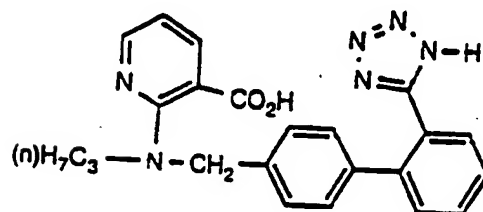
Source

320

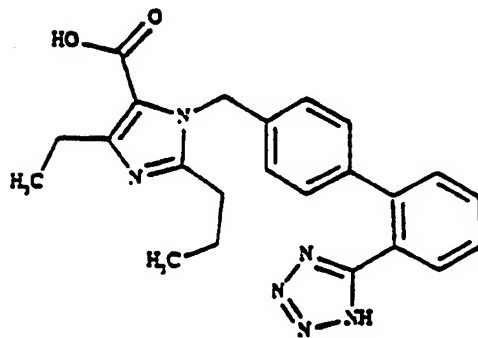


US #5,015,651  
pub. 14 May 91

321

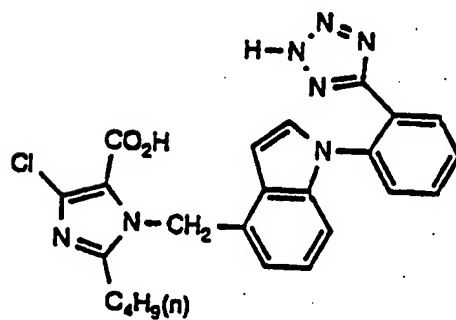


322



WO #92/00977  
pub. 23 Jan 92

323



132

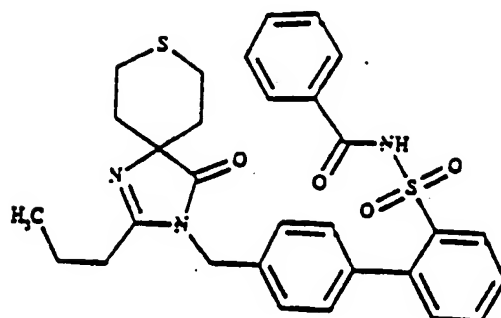
TABLE II: Angiotensin II Antagonists

Compound #

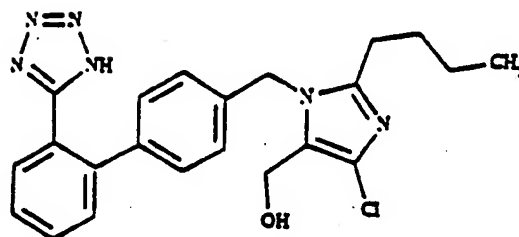
Structure

Source

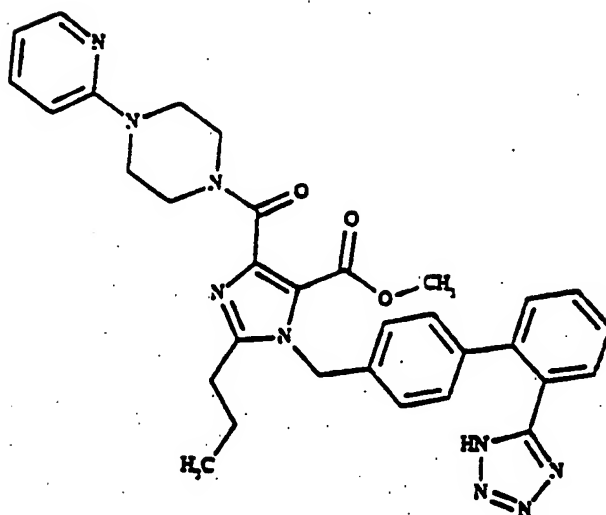
324

WO #93/04046  
pub. 04 Mar 93

325

WO #93/10106  
pub. 27 May 93

326

US #5,219,856  
pub. 15 Jun 93

133

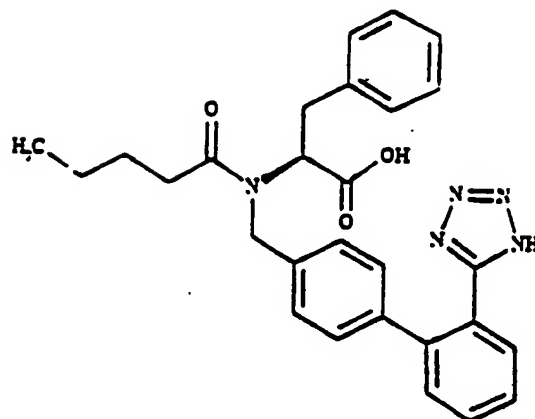
TABLE II: Angiotensin II Antagonists

Compound #

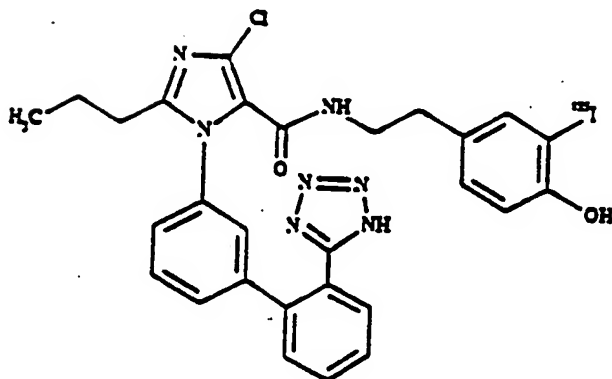
Structure

Source

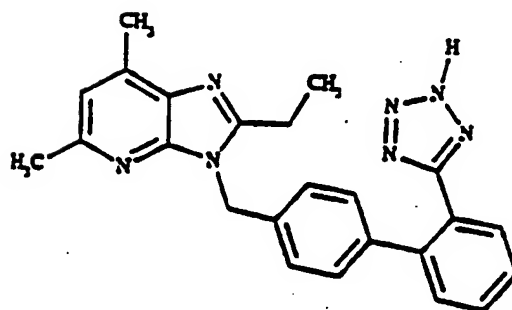
327

US #5,260,325  
pub. 09 Nov 93

328

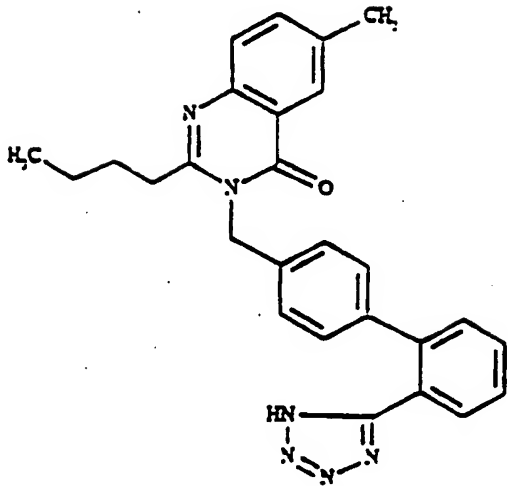
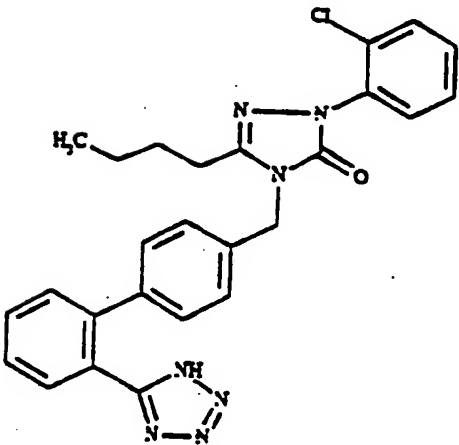
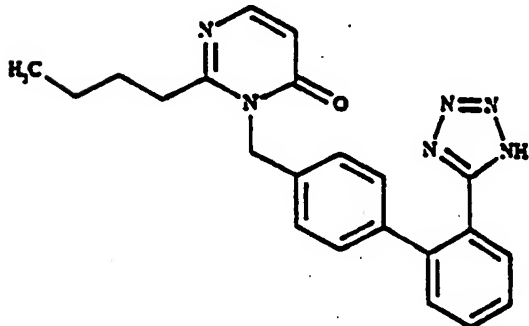
US #5,264,581  
pub. 23 Nov 93

329

EP #400,974  
pub. 05 Dec 90

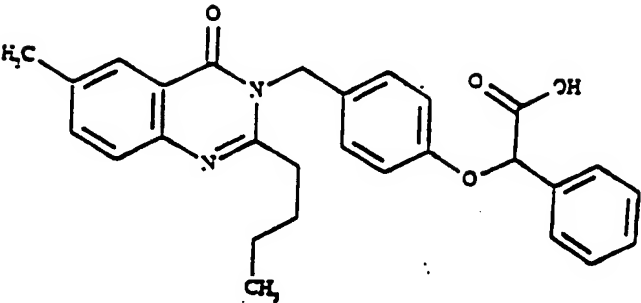
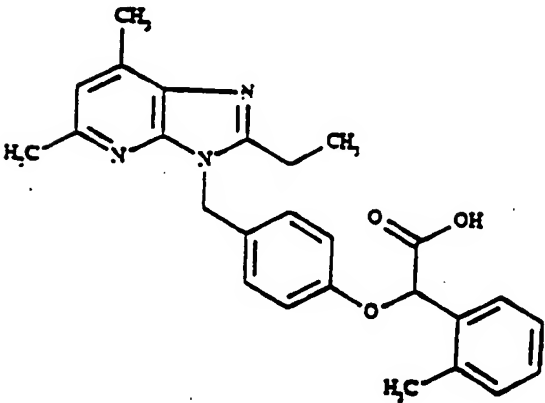
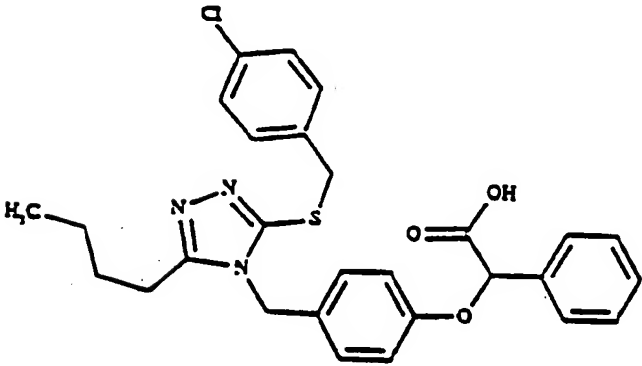
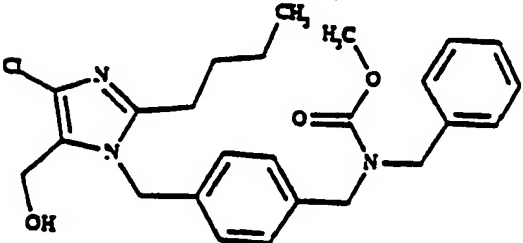
134

TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                        |
|------------|--|-------------------------------|
| 330        |    | EP #411,766<br>pub. 06 Feb 91 |
| 331        |   | EP #412,594<br>pub. 13 Feb 91 |
| 332        |  | EP #419,048<br>pub. 27 Mar 91 |

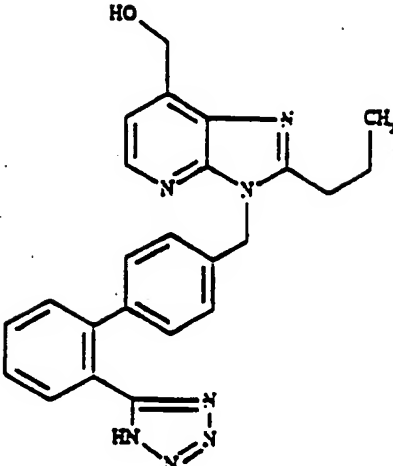
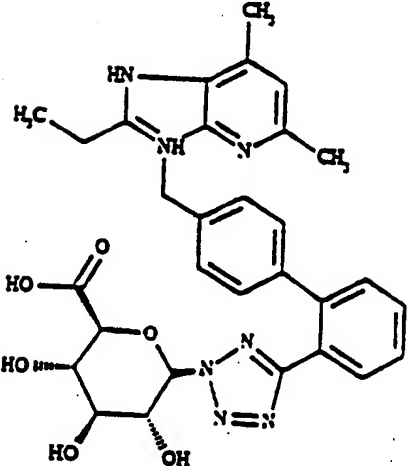
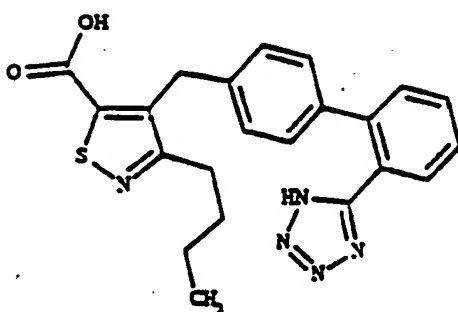
135

TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                          |
|------------|--|---------------------------------|
| 333        |    | WO #91/12,001<br>pub. 22 Aug 91 |
| 334        |   | WO #91/11,999<br>pub. 22 Aug 91 |
| 335        |  | WO #91/11,909<br>pub. 22 Aug 91 |
| 336        |  | WO #91/12,002<br>pub. 22 Aug 91 |

136

TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                          |
|------------|---|---------------------------------|
| 337        |    | US #5,053,329<br>pub. 01 Oct 91 |
| 338        |   | US #5,057,522<br>pub 15 Oct 91  |
| 339        |  | WO #91/15,479<br>pub. 17 Oct 91 |

137

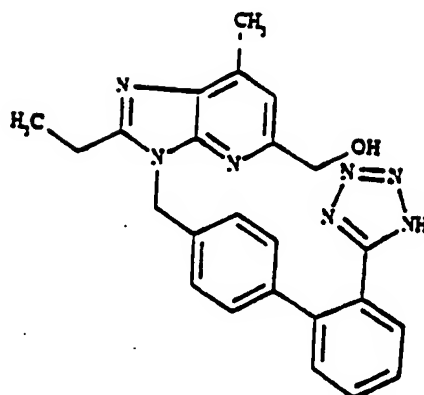
TABLE II: Angiotensin II Antagonists

Compound #

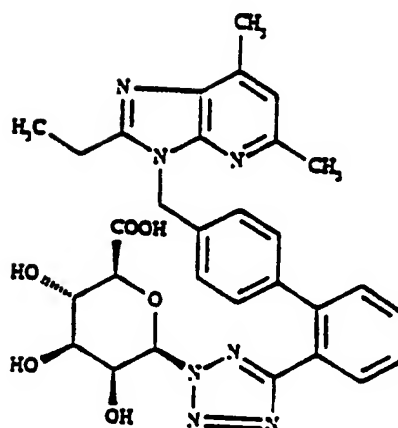
Structure

Source

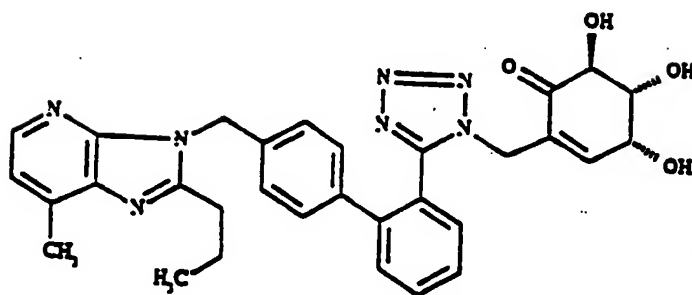
340

EP #456,510  
pub. 13 Nov 91

341

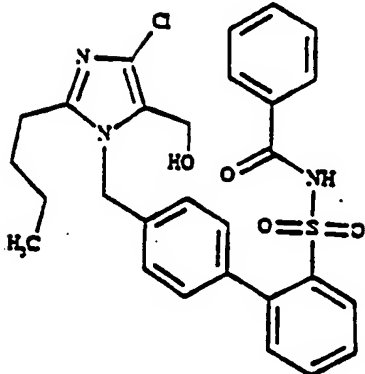
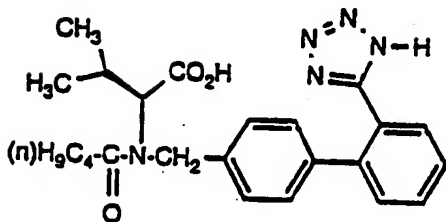
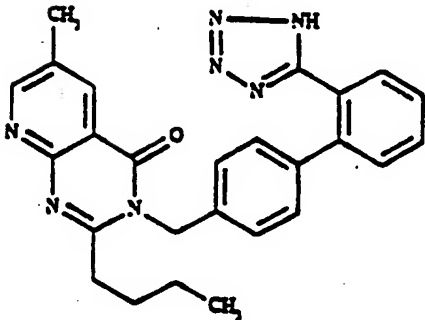
EP #467,715  
pub. 22 Jan 92

342

US #5,087,702  
pub. 11 Feb 92

138

TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                        |
|------------|---|-------------------------------|
| 343        |    | EP #479,479<br>pub. 08 Apr 92 |
| 344        |   |                               |
| 345        |  | EP #481,614<br>pub. 22 Apr 92 |



139

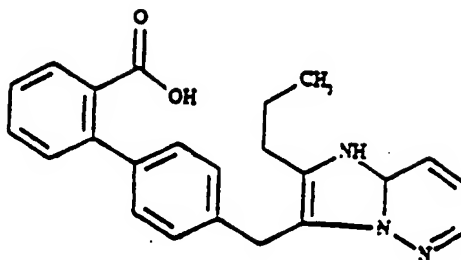
TABLE II: Angiotensin II Antagonists

Compound #

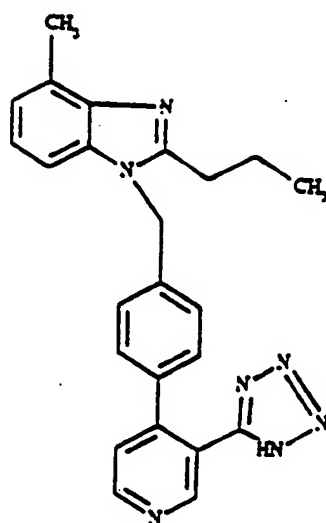
Structure

Source

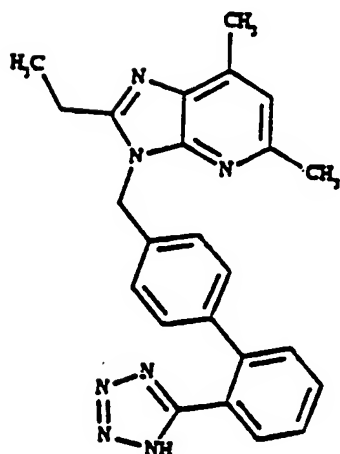
346

EP #490,587  
pub. 17 Jun 92

347

US #5,128,327  
pub. 07 Jul 92

348

US #5,132,216  
pub. 21 Jul 92

140

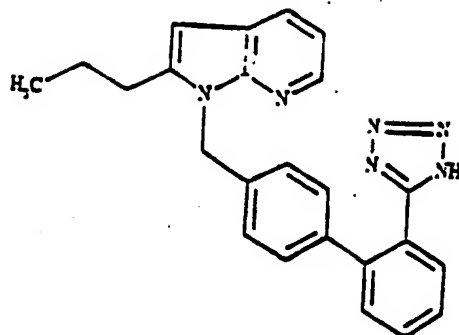
TABLE II: Angiotensin II Antagonists

Compound #

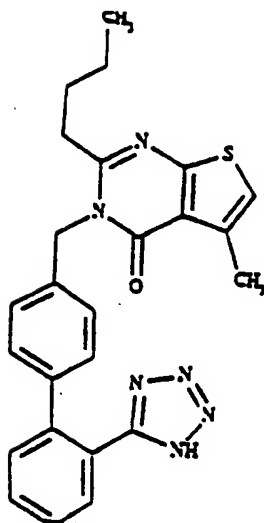
Structure

Source

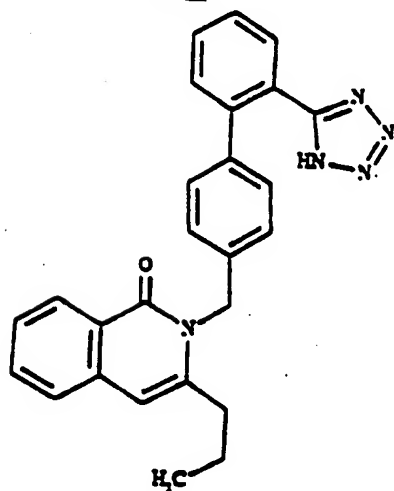
349

EP #497,516  
pub. 05 Aug 92

350

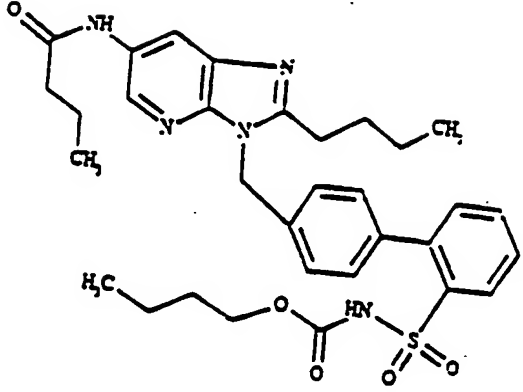
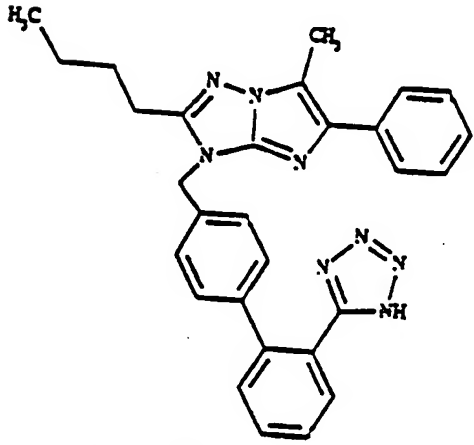
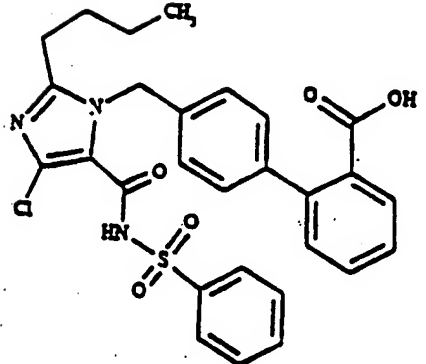
EP #502,725  
pub. 09 Sep 92

351

EP #502,575  
pub. 09 Sep 92

141

TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                        |
|------------|---|-------------------------------|
| 352        |   | EP #503,838<br>pub. 16 Sep 92 |
| 353        |   | EP #505,111<br>pub. 23 Sep 92 |
| 354        |  | EP #505,098<br>pub. 23 Sep 92 |

142

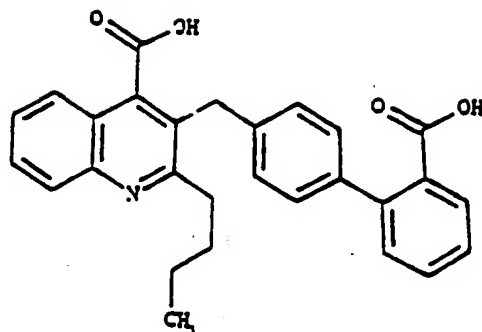
TABLE II: Angiotensin II Antagonists

Compound #

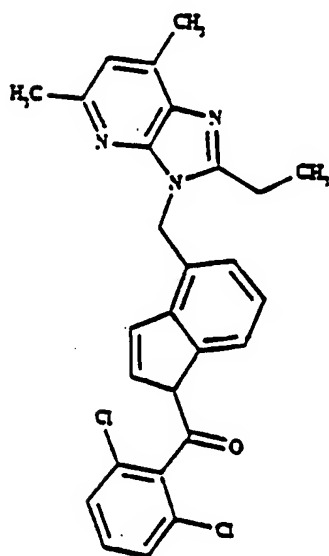
Structure

Source

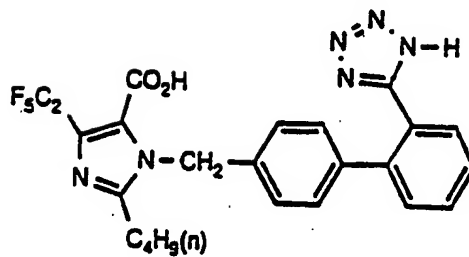
355

EP #507,594  
pub. 07 Oct 92

356

EP #508,723  
pub. 14 Oct 92

357



143

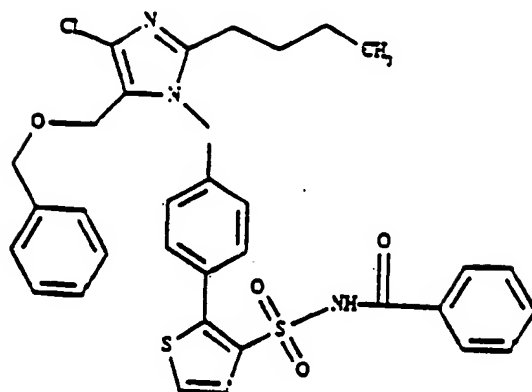
TABLE II: Angiotensin II Antagonists

Compound #

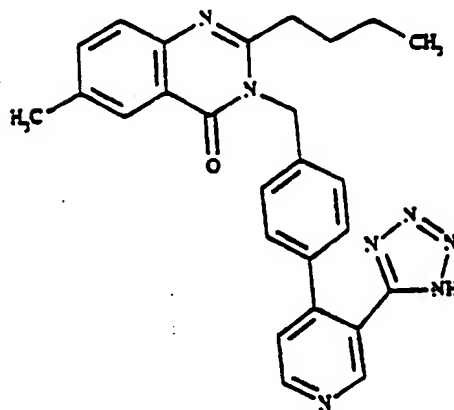
Structure

Source

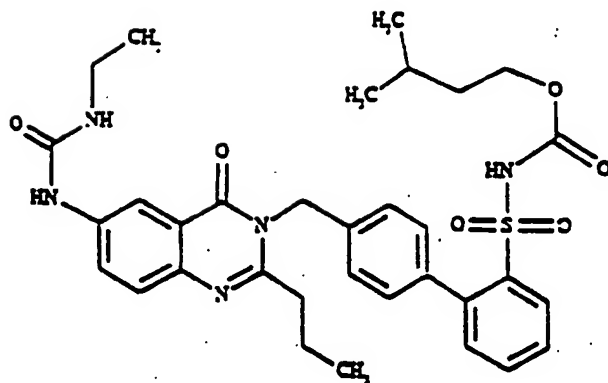
358

EP #512,675  
pub. 11 Nov 92

359

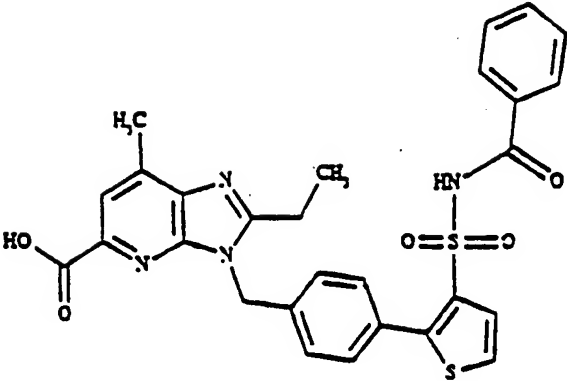
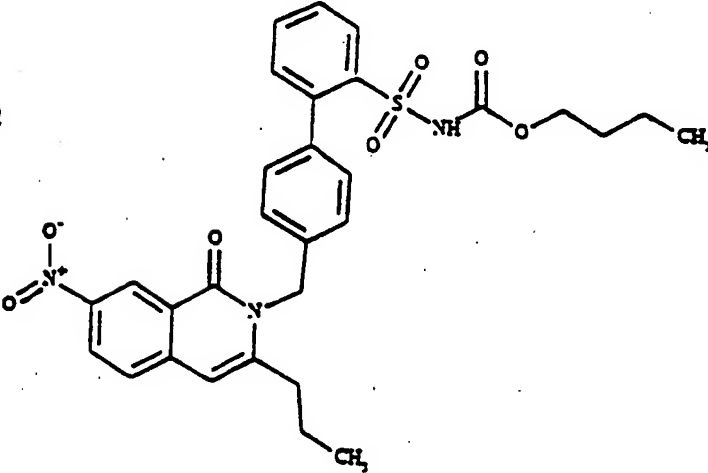
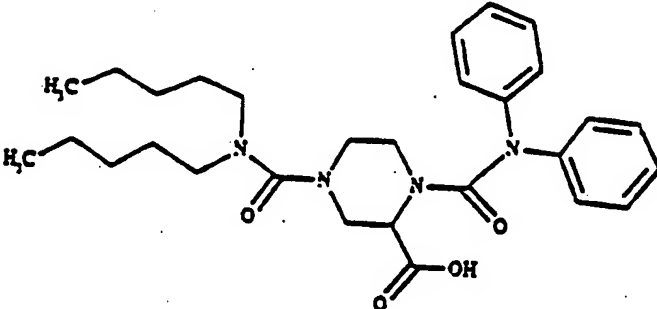
EP #512,676  
pub. 11 Nov 92

360

EP #512,870  
pub. 11 Nov 92

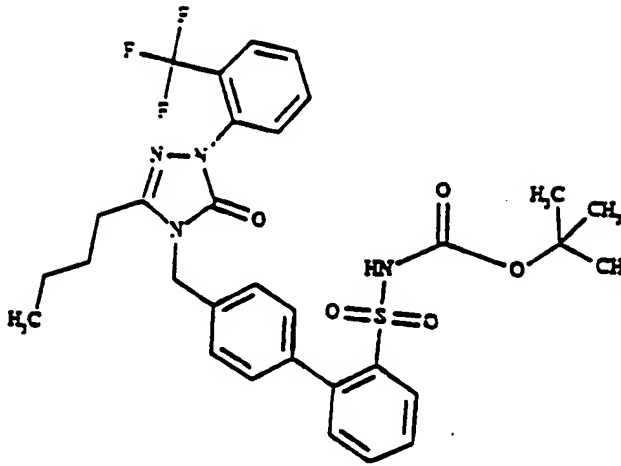
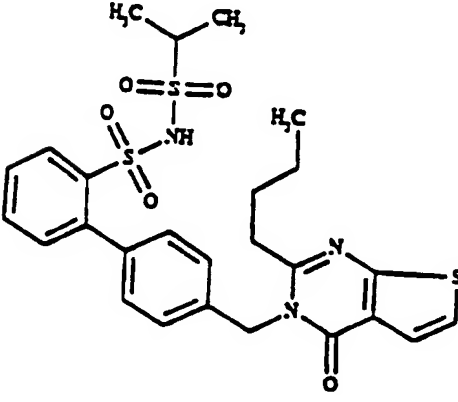
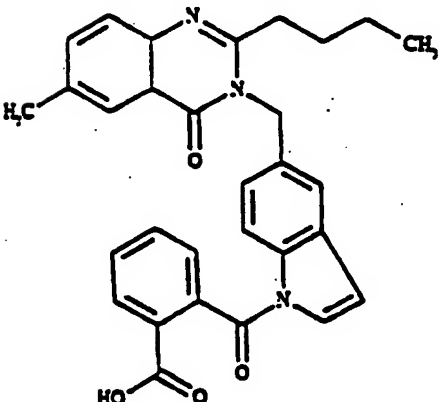
144

TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                          |
|------------|--|---------------------------------|
| 361        |    | EP #513,979<br>pub. 19 Nov 92   |
| 362        |   | WO #92/20,660<br>pub. 26 Nov 92 |
| 363        |  | WO #92,20,661<br>pub. 26 Nov 92 |

145

TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                          |
|------------|---|---------------------------------|
| 364        |   | WO #92/20,662<br>pub. 26 Nov 92 |
| 365        |   | WO #92/20,687<br>pub. 26 Nov 92 |
| 366        |  | EP #517,357<br>pub. 09 Dec 92   |

146

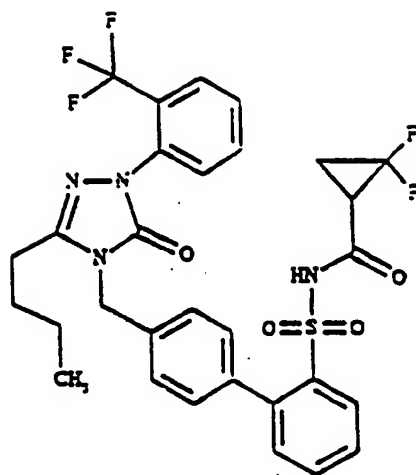
TABLE II: Angiotensin II Antagonists

Compound #

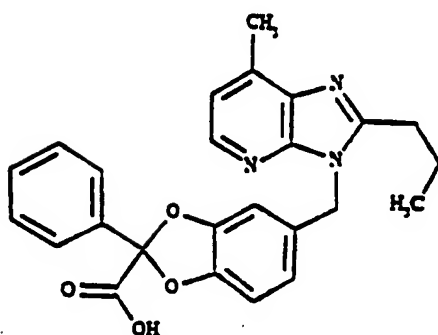
Structure

Source

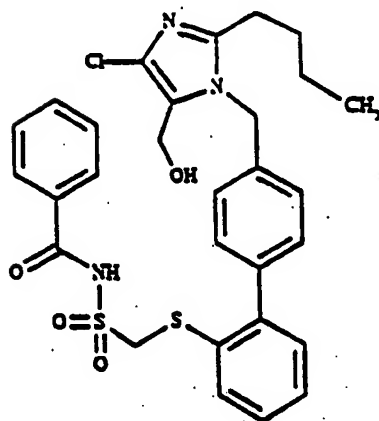
367

WO #93/01177  
pub. 21 Jan 93

368

US #5,187,159  
pub. 16 Feb 93

369

US #5,198,438  
pub. 30 Mar 93



147

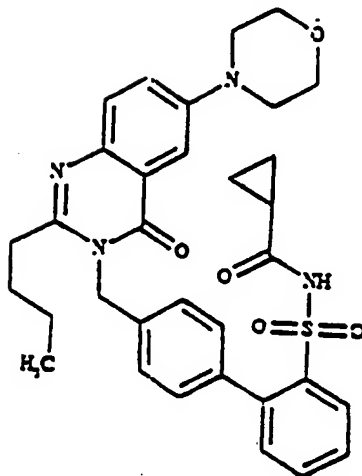
TABLE II: Angiotensin II Antagonists

Compound #

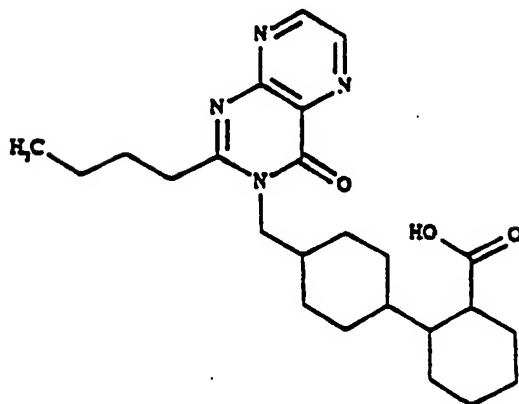
Structure

Source

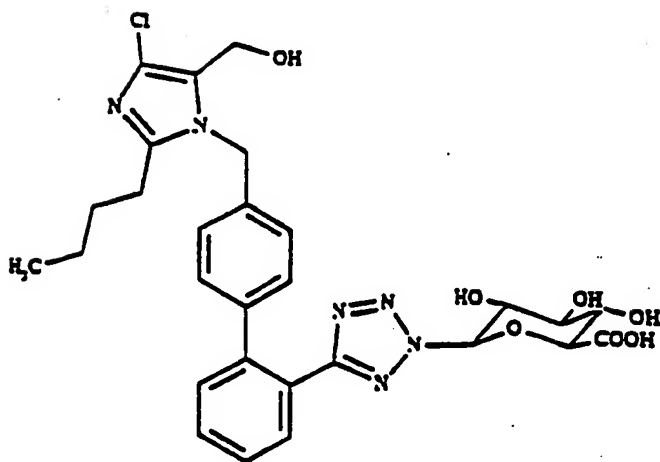
370

US #5,202,322  
pub. 13 Apr 93

371

EP #537,937  
pub. 21 Apr 93

372

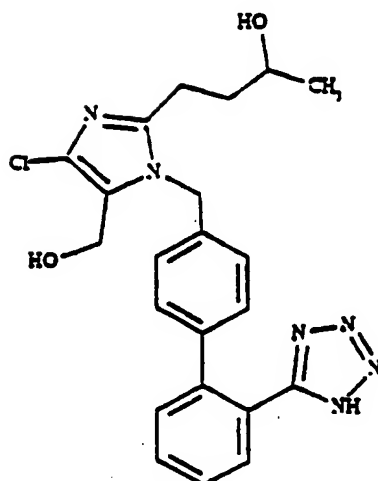
US #5,217,882  
pub. 08 Jun 93

148

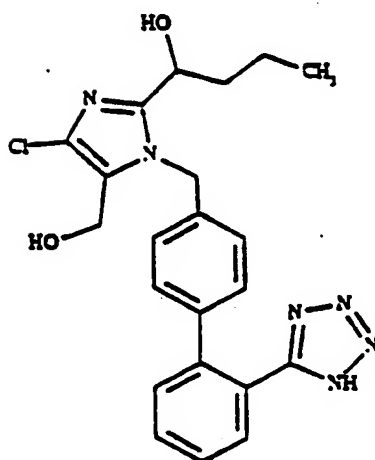
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

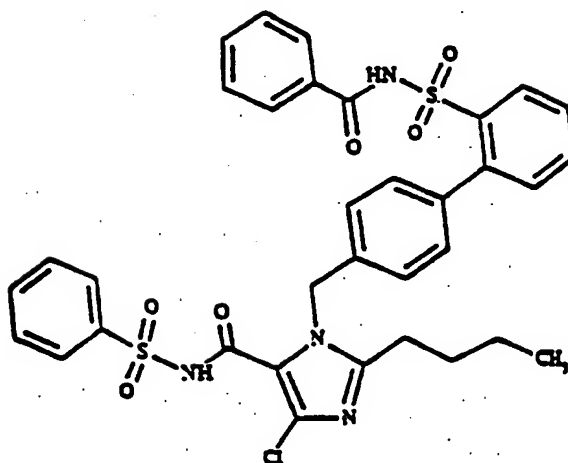
373

US #5,214,153  
pub. 25 May 93

374

US #5,218,125  
pub. 08 Jun 93

375

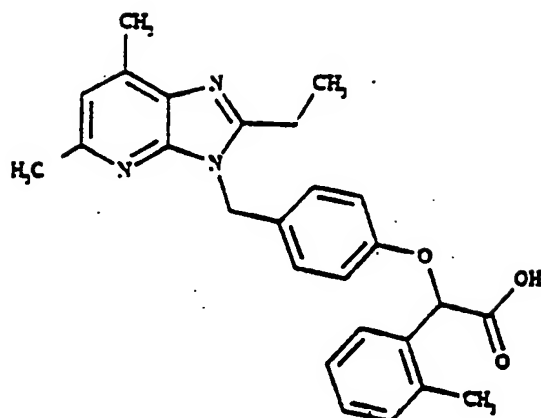
US #5,236,928  
pub. 17 Aug 93

149

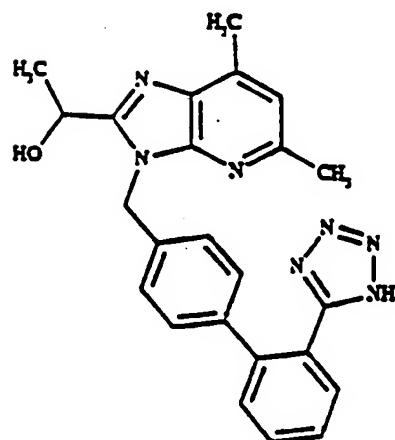
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

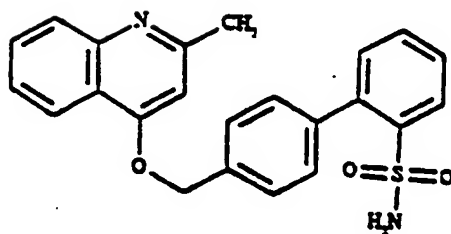
376

US #5,240,938  
pub. 31 Aug 93

377

GB #2,264,709  
pub. 08 Sep 93

378

GB #2,264,710  
pub. 08 Sep 93

150

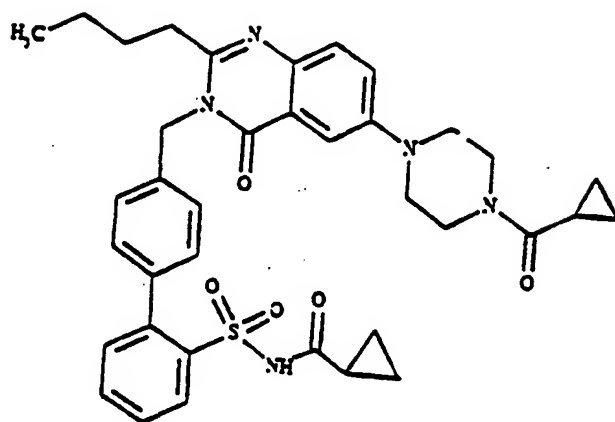
TABLE II: Angiotensin II Antagonists

Compound #

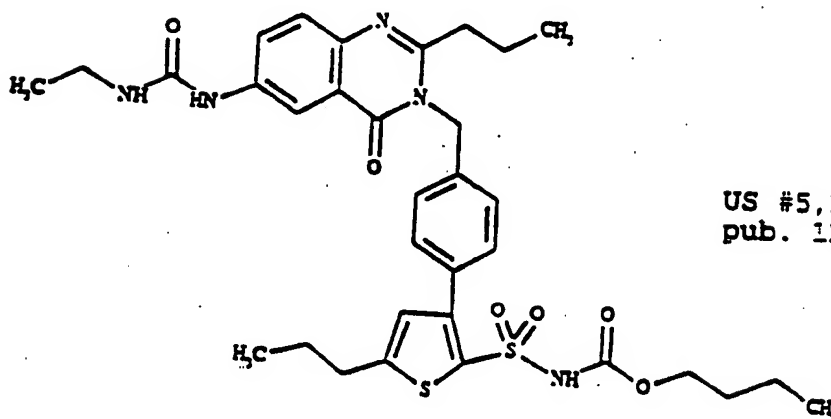
Structure

Source

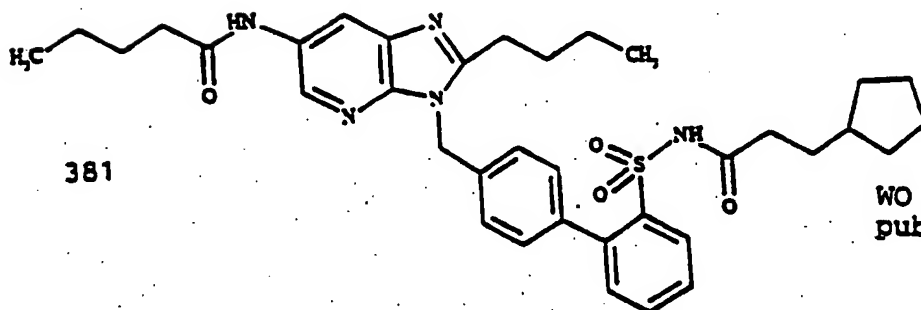
379

US #5,256,667  
pub. 26 Oct 93

380

US #5,525,574  
pub. 12 Oct 93

381

WO #93/23,399  
pub. 25 Nov 93



152

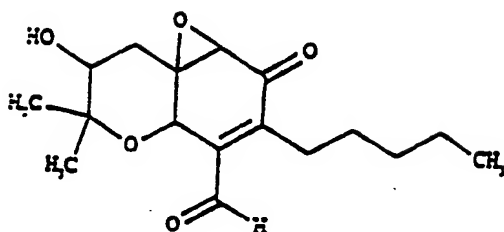
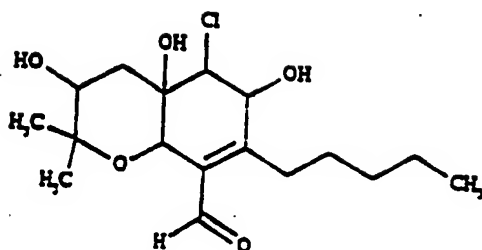
TABLE II: Angiotensin II Antagonists

Compound #

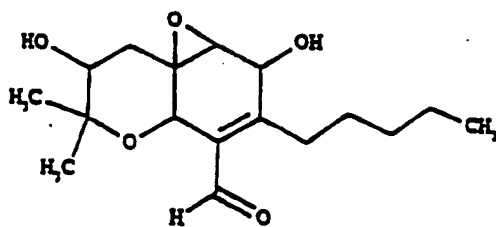
Structure

Source

385

US #5,276,054  
pub. 04 Jan 94

386

US #5,278,068  
pub. 11 Jan 94

153

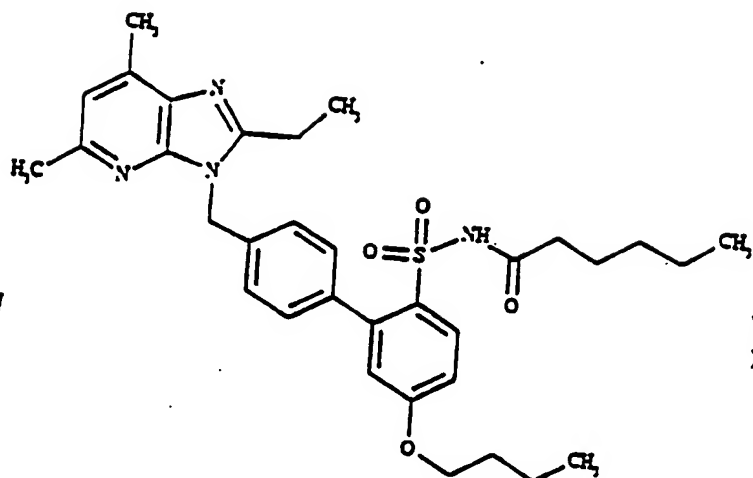
TABLE II: Angiotensin II Antagonists

Compound #

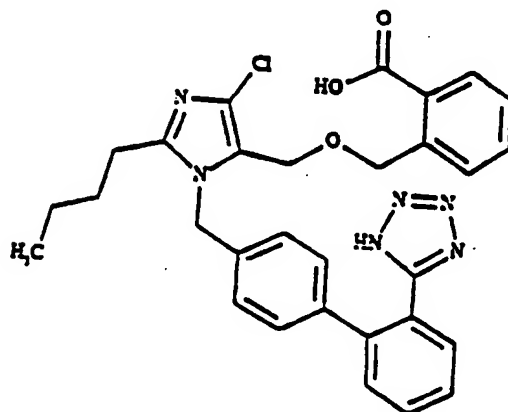
Structure

Source

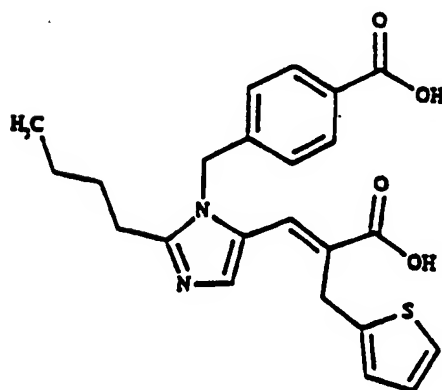
387

WO #94/02142  
pub. 03 Feb 94

388

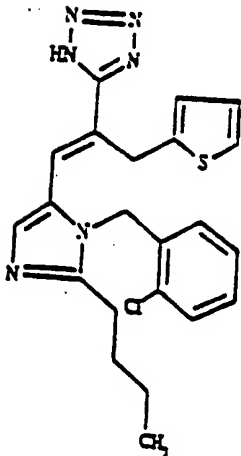
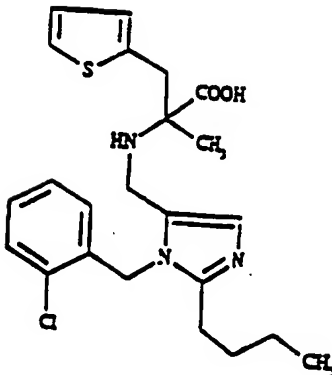
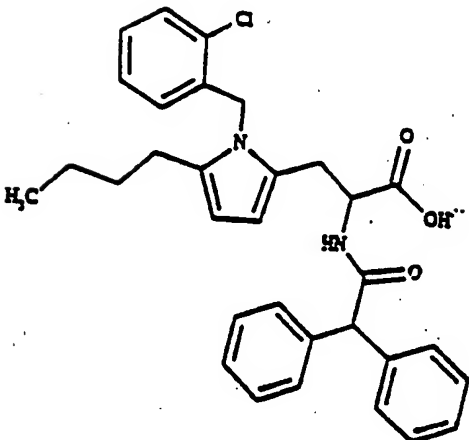
WO #94/02467  
pub. 03 Feb 94

389

EP #403,159  
pub. 19 Dec 90

154

TABLE II: Angiotensin II Antagonists

| Compound # | Structure   | Source                         |
|------------|---|--------------------------------|
| 390        |    | EP #425,211<br>pub. 02 May 91  |
| 391        |   | EP #427,463<br>pub 15 May 91   |
| 392        |  | WO #92/00068<br>pub. 09 Jan 92 |

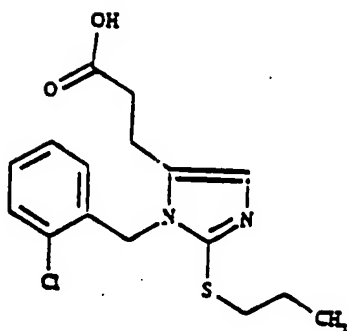


155

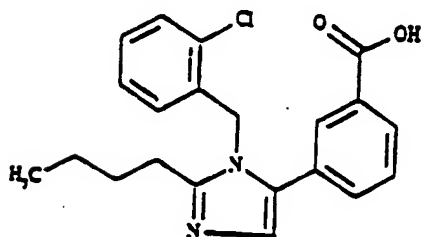
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

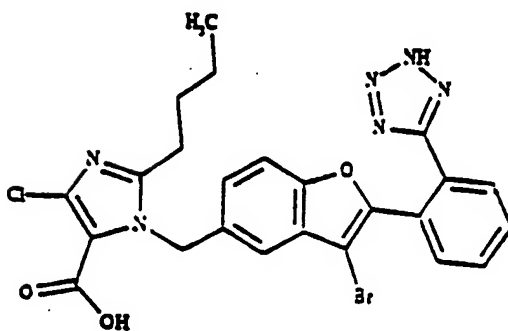
393

WO #92/02,510  
pub. 20 Feb 92

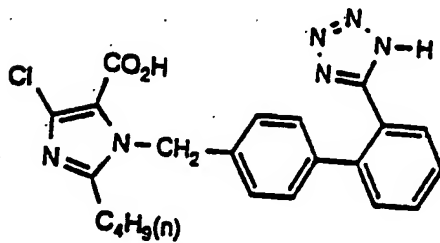
394

WO #92/09278  
pub. 11 Jun 92

395

WO #92/10181  
pub. 25 Jun 92

396

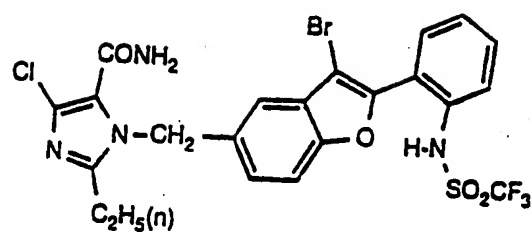


156

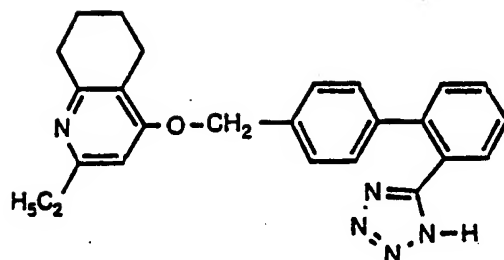
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

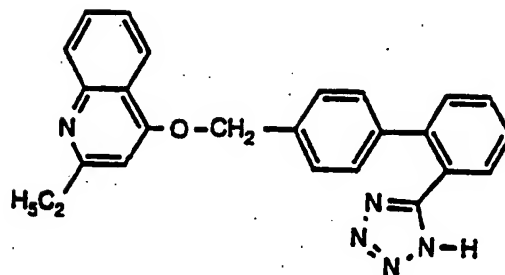
397



398



399

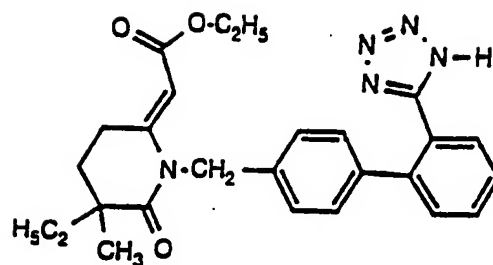


157

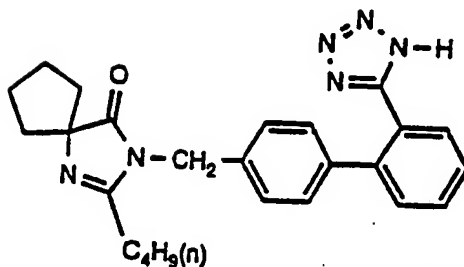
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

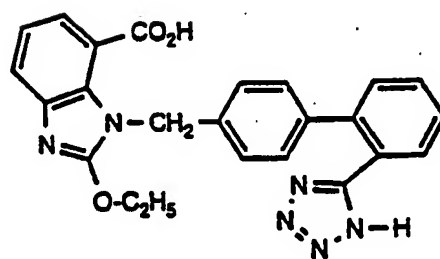
400



401



402

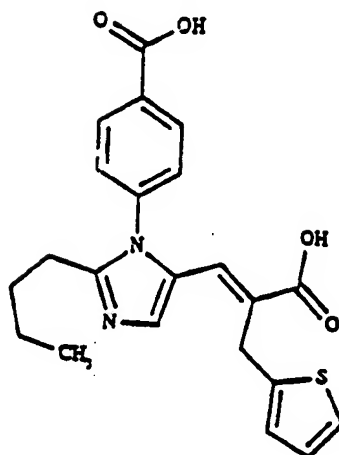


158

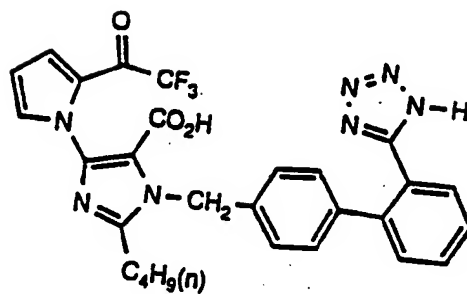
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

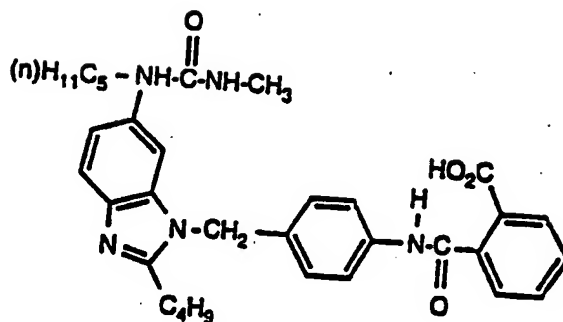
403

WO #92/10097  
pub. 25 Jun 92

404



405

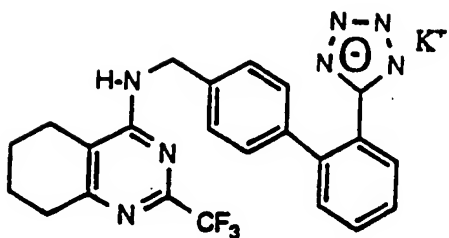


159

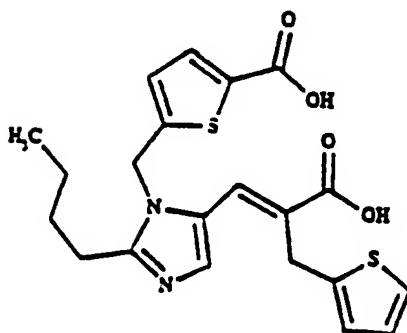
TABLE II: Angiotensin II Antagonists

| Compound # | Structure | Source |
|------------|-----------|--------|
|------------|-----------|--------|

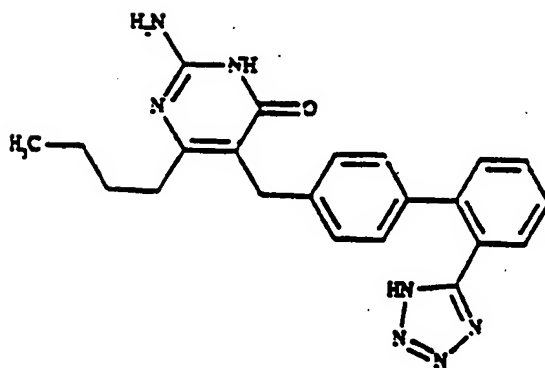
406



407

WO #92/20651  
pub. 26 Nov 92

408

WO #93/03018  
pub. 18 Feb 93

160

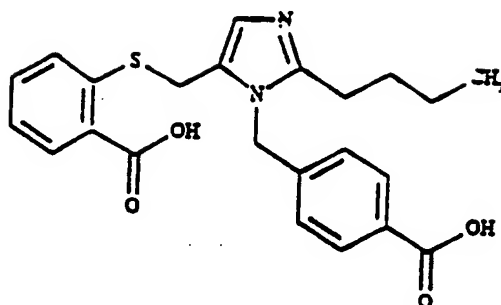
TABLE II: Angiotensin II Antagonists

Compound #

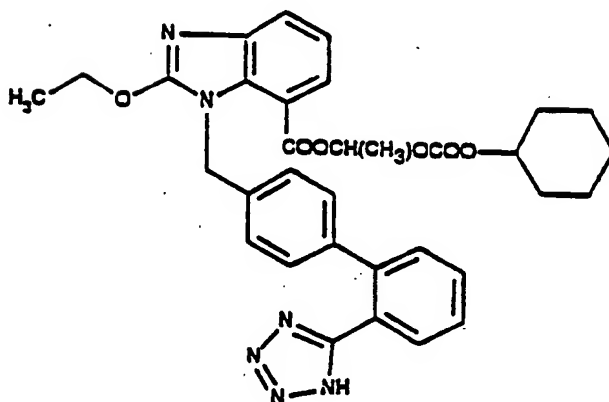
Structure

Source

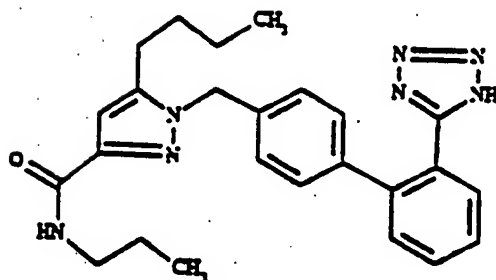
409

WO #94/00120  
pub. 06 Jan 94

410

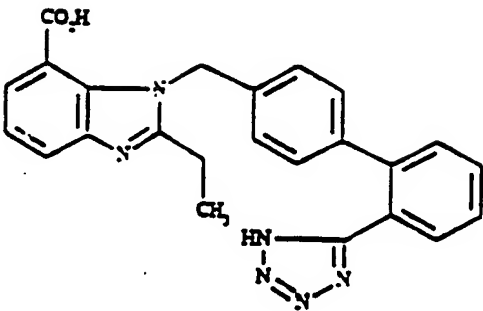
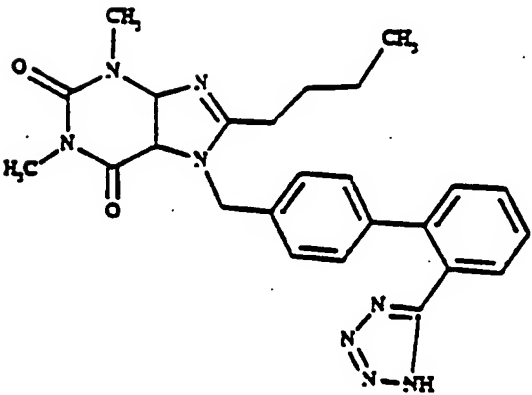
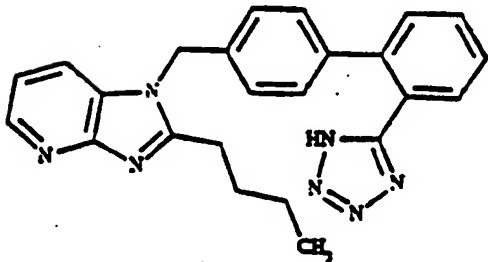
EP #459,136  
pub. 04 Dec 91

411

EP #411,507  
pub. 05 Feb 91

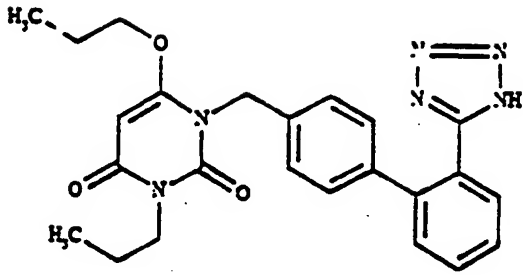
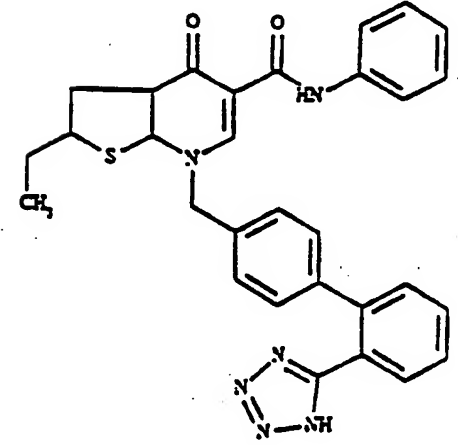
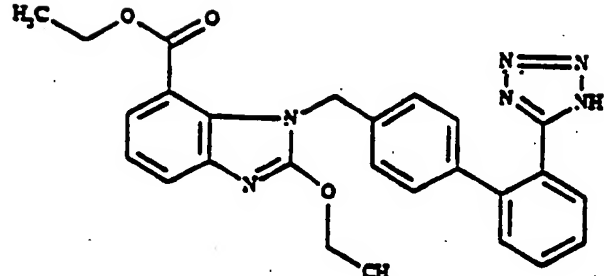
161

TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                        |
|------------|--|-------------------------------|
| 412        |    | EP #425,921<br>pub. 08 May 91 |
| 413        |   | EP #430,300<br>pub. 05 Jun 91 |
| 414        |  | EP #434,038<br>pub. 26 Jun 91 |

162

TABLE II: Angiotensin II Antagonists

| Compound # | Structure  | Source                        |
|------------|--|-------------------------------|
| 415        |    | EP #442,473<br>pub. 21 Aug 91 |
| 416        |   | EP #443,568<br>pub. 28 Aug 91 |
| 417        |  | EP #459,136<br>pub. 04 Dec 91 |



163

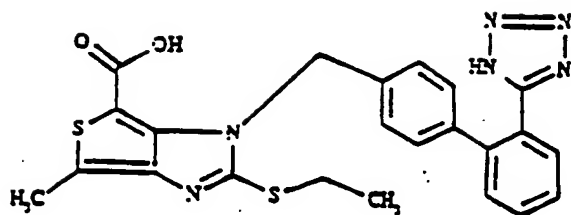
TABLE II: Angiotensin II Antagonists

Compound #

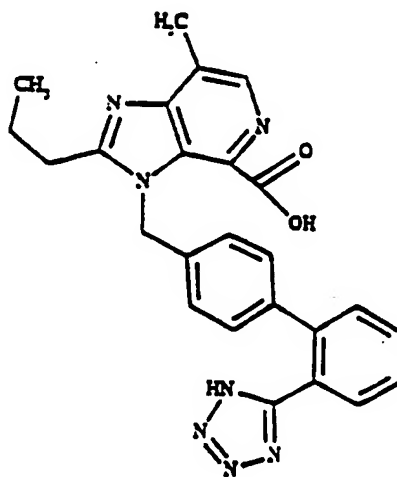
Structure

Source

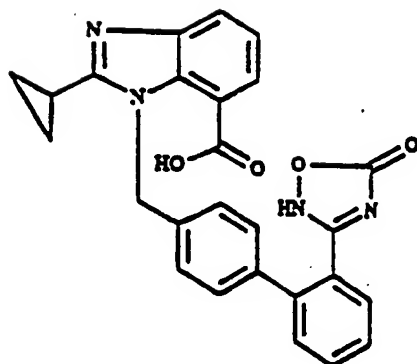
418

EP #483,683  
pub. 05 May 92

419

EP #518,033  
pub. 16 Dec 92

420

EP #520,423  
pub. 30 Dec 92

164

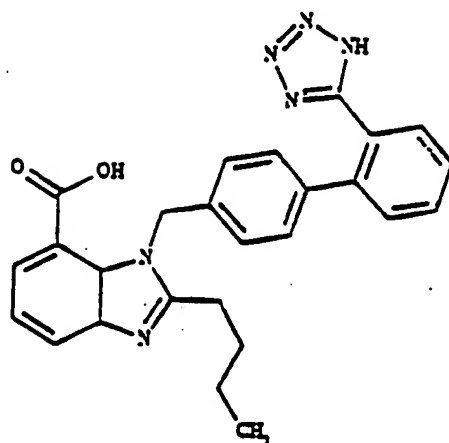
TABLE II: Angiotensin II Antagonists

Compound #

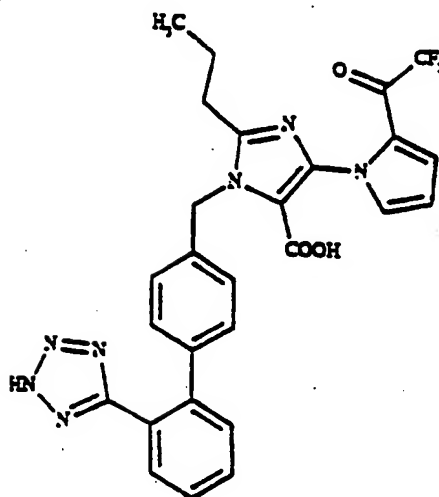
Structure

Source

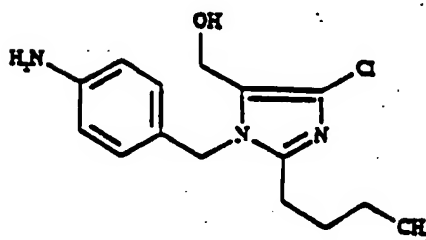
421

EP #546,358  
pub. 16 Jun 93

422

WO #93/00341  
pub. 07 Jan 93

423

WO #92/06081  
pub. 16 Apr 92

165

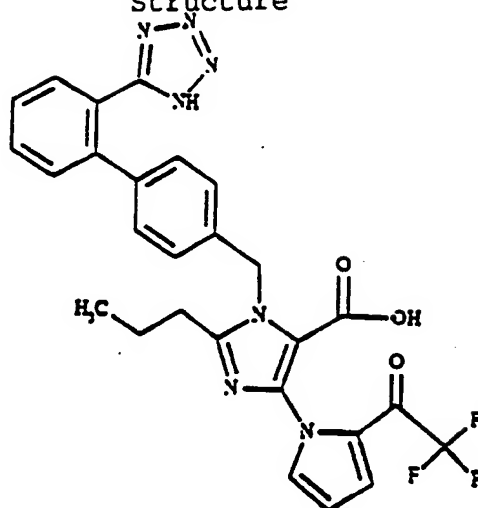
TABLE II: Angiotensin II Antagonists

Compound #

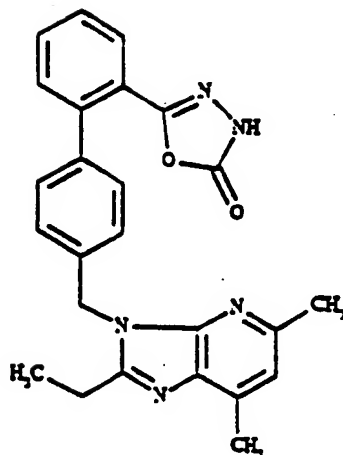
Structure

Source

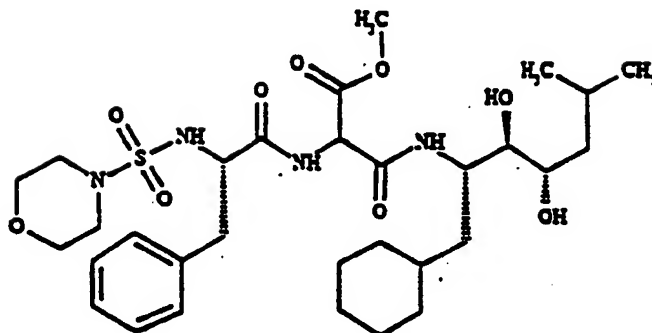
424

WO #93/00341  
pub. 07 Jan 93

425

US #5,210,204  
pub. 11 May 93

426

EP #343,654  
pub. 29 Nov 89

166

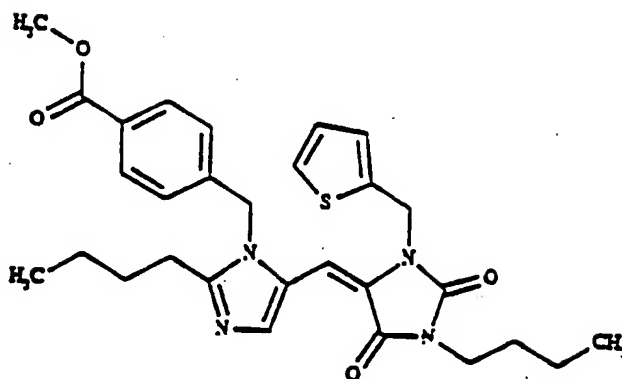
TABLE II: Angiotensin II Antagonists

Compound #

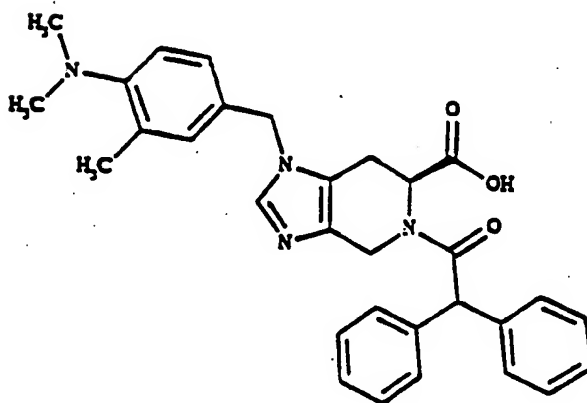
Structure

Source

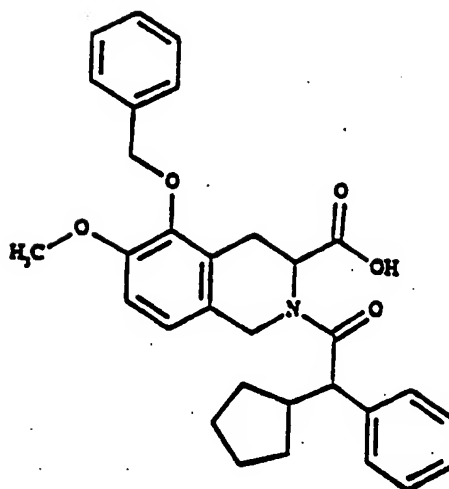
427

WO #93/13077  
pub. 08 Jul 93

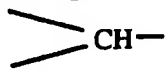
428

WO #93/15734  
pub. 19 Aug 93

429

US #5,246,943  
pub. 21 Sep 93

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or, as another example, one hydrido group may be attached to a carbon atom

5 to form a  group; or, as another example, two hydrido atoms may be attached to a carbon atom to form a -CH<sub>2</sub>- group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched  
10 radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The  
15 term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is  
20 substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a  
25 fluoro atom within the group. Dihalalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two  
30 chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl groups. The term "difluoroalkyl" embraces alkyl groups having two fluoro atoms substituted on  
35 any one or two of the alkyl group carbon atoms. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched

alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenyl-ethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "phenalkyl" and "phenylalkyl" are interchangeable. An example of "phenalkyl" is "phenethyl" which is interchangeable with "phenylethyl". The terms "alkylaryl", "alkoxyaryl" and "haloaryl" denote, respectively, the substitution of one or more "alkyl",

"alkoxy" and "halo" groups, respectively, substituted on an "aryl" nucleus, such as a phenyl moiety. The terms "aryloxy" and "arylthio" denote radicals respectively, provided by aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes, respectively, divalent radicals SO and SO<sub>2</sub>. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. "Lower alkanoyl" is an example of a more preferred sub-class of acyl. The term "amido" denotes a radical consisting of nitrogen atom attached to a carbonyl group, which radical may be further substituted in the manner described herein. The term "monoalkylaminocarbonyl" is interchangeable with "N-alkylamido". The term "dialkylaminocarbonyl" is interchangeable with "N,N-dialkylamido". The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted with alkyl groups which may optionally contain additional double-bond unsaturation. The term "heteroaryl", where not otherwise defined before, embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity

of the heteroaryl moiety is preserved after attachment. For any of the foregoing defined radicals, preferred radicals are those containing from one to about ten carbon atoms.

5                Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a  
10                plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

                 Also included in the combination of the invention  
15                are the isomeric forms of the above-described angiotensin II receptor compounds and the epoxy-steroidal aldosterone receptor compounds, including diastereoisomers, regioisomers and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly  
20                used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid.  
25                Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic  
30                acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicylic, phenylacetic, mandelic,  
35                embonic (pamoic), methansulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic,



cyclohexylaminosulfonic, stearic, algenic,  $\beta$ -hydroxybutyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts include metallic salts made from aluminium, calcium, lithium, 5 magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by 10 conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with such compound.

### BIOLOGICAL EVALUATION

Human congestive heart failure (CHF) is a complex  
5 condition usually initiated by vascular hypertension or a  
myocardial infarction (MI). In order to determine the  
probable effectiveness of a combination therapy for CHF, it  
is important to determine the potency of individual  
components of the combination therapy. Accordingly, in  
10 Assays "A" through "C", the angiotensin II receptor  
antagonist profiles were determined for many of the  
compounds described in Table II, herein. In Assays "D" and  
"E", there are described methods for evaluating a  
combination therapy of the invention, namely, an angiotensin  
15 II receptor antagonist of Table II and an epoxy-steroidal  
aldosterone receptor antagonist of Table I. The efficacy of  
the individual drugs, epoxymexrenone and the angiotensin II  
receptor blocker, and of these drugs given together at  
various doses, are evaluated in rodent models of  
20 hypertension and CHF using surgical alterations to induce  
either hypertension or an MI. The methods and results of  
such assays are described below.

#### Assay A: Angiotensin II Binding Activity

25

Compounds of the invention were tested for ability  
to bind to the smooth muscle angiotensin II receptor using a  
rat uterine membrane preparation. Angiotensin II (AII) was  
purchased from Peninsula Labs.  $^{125}\text{I}$ -angiotensin II (specific  
30 activity of 2200 Ci/mmol) was purchased from Du Pont-New  
England Nuclear. Other chemicals were obtained from Sigma  
Chemical Co. This assay was carried out according to the  
method of Douglas et al [Endocrinology, 106, 120-124  
(1980)]. Rat uterine membranes were prepared from fresh  
35 tissue. All procedures were carried out at 4°C. Uteri were  
stripped of fat and homogenized in phosphate-buffered saline  
at pH 7.4 containing 5 mM EDTA. The homogenate was

centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM MgCl<sub>2</sub>, 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and <sup>125</sup>I-AII (approximately 10<sup>5</sup> cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 µM of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC<sub>50</sub>) of the tested AII antagonist which gives 50% displacement of the total specifically bound <sup>125</sup>I-AII from the angiotensin II AT<sub>1</sub> receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table III.

25

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

The compounds of the invention were tested for antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a

stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled with 20 ml of oxygenated (95% oxygen/5% carbon dioxide)

5 Krebs solution of the following composition (mM): 130 NaCl, 15 NaHCO<sub>3</sub>, 15 KCl, 1.2 NaH<sub>2</sub>PO<sub>4</sub>, 1.2 MgSO<sub>4</sub>, 2.5 CaCl<sub>2</sub>, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response  
10 curves were then recorded ( $3 \times 10^{-10}$  to  $1 \times 10^{-5}$  M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at  $10^{-5}$   
15 M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA<sub>2</sub> values and were calculated  
20 according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The pA<sub>2</sub> value is the concentration of the antagonist which increases the EC<sub>50</sub> value for AII by a factor of two. Each test antagonist was evaluated in aorta rings from two rabbits. Results are reported in Table III.

25

Assay C: In Vivo Intragastric Pressor Assay Response for All Antagonists

Male Sprague-Dawley rats weighing 225-300 grams  
30 were anesthetized with methohexital (30 mg/kg, i.p.) and catheters were implanted into the femoral artery and vein. The catheters were tunneled subcutaneously to exit dorsally, posterior to the head and between the scapulae. The catheters were filled with heparin (1000 units/ml of  
35 saline). The rats were returned to their cage and allowed regular rat chow and water ad libitum. After full recovery from surgery (3-4 days), rats were placed in Lucite holders

and the arterial line was connected to a pressure transducer. Arterial pressure was recorded on a Gould polygraph (mmHg). Angiotensin II was administered as a 30 ng/kg bolus via the venous catheter delivered in a 50  $\mu$ l volume with a 0.2 ml saline flush. The pressor response in mm Hg was measured by the difference from pre-injection arterial pressure to the maximum pressure achieved. The AII injection was repeated every 10 minutes until three consecutive injections yielded responses within 4 mmHg of each other. These three responses were then averaged and represented the control response to AII. The test compound was suspended in 0.5% methylcellulose in water and was administered by gavage. The volume administered was 2 ml/kg body weight. The standard dose was 3 mg/kg. Angiotensin II bolus injections were given at 30, 45, 60, 75, 120, 150, and 180 minutes after gavage. The pressor response to AII was measured at each time point. The rats were then returned to their cage for future testing. A minimum of 3 days was allowed between tests. Percent inhibition was calculated for each time point following gavage by the following formula:  $[(\text{Control Response} - \text{Response at time point}) / \text{Control Response}] \times 100$ . Results are shown in Table III.

25 Assay "D": Hypertensive Rat Model

Male rats are made hypertensive by placing a silver clip with an aperture of 240 microns on the left renal artery, leaving the contralateral kidney untouched. Sham controls undergo the same procedure but without attachment of the clip. One week prior to the surgery, animals to be made hypertensive are divided into separate groups and drug treatment is begun. Groups of animals are administered vehicle, AII antagonist alone, epoxymexrenone alone, and combinations of AII antagonist and epoxymexrenone at various doses:

| AII Antagonist<br>(mg/kg/day) | Epoymexrenone<br>(mg/kg/day) | Combination of<br>AII Antagonist & Epoymexrenone |             |
|-------------------------------|------------------------------|--|-------------|
|                               |                              | (mg/kg/day)                                      | (mg/kg/day) |
| 3                             | 5                            | 3  | 5           |
|                               | 20                           | 3  | 20          |
|                               | 50                           | 3  | 50          |
|                               | 100                          | 3  | 100         |
|                               | 200                          | 3  | 200         |
| 10                            | 5                            | 10   | 5           |
|                               | 20                           | 10   | 20          |
|                               | 50                           | 10   | 50          |
|                               | 100                          | 10   | 100         |
|                               | 200                          | 10   | 200         |
| 30                            | 5                            | 30   | 5           |
|                               | 20                           | 30   | 20          |
|                               | 50                           | 30   | 50          |
|                               | 100                          | 30   | 100         |
|                               | 200                          | 30   | 200         |

After 12 to 24 weeks, systolic and diastolic blood pressure, left ventricular end diastolic pressure, left ventricular dP/dt, and heart rate are evaluated. The hearts are removed, weighed, measured and fixed in formalin. Collagen content of heart sections are evaluated using computerized image analysis of picrosirius stained sections. It would be expected that rats treated with a combination therapy of AII antagonist and epoymexrenone components, as compared to rats treated with either component alone, will show improvements in cardiac performance.

Assay "E": Myocardial Infarction Rat Model:

15

Male rats are anesthetized and the heart is exteriorized following a left sided thoracotomy. The left anterior descending coronary artery is ligated with a suture. The thorax is closed and the animal recovers. Sham

animals have the suture passed through without ligation. One week prior to the surgery, animals to undergo infarction are divided into separate groups and drug treatment is begun. Groups of animals are administered vehicle, AII antagonist alone, epoxymexrenone alone, and combinations of AII antagonist and epoxymexrenone, at various doses, as follow:

| AII Antagonist<br>(mg/kg/day) | Epoxymexrenone<br>(mg/kg/day) | Combination of<br>AII Antagonist & Epoxymexrenone |             |
|-------------------------------|-------------------------------|---|-------------|
|                               |                               | (mg/kg/day)                                       | (mg/kg/day) |
| 3                             | 5                             | 3   | 5           |
|                               | 20                            | 3   | 20          |
|                               | 50                            | 3   | 50          |
|                               | 100                           | 3   | 100         |
|                               | 200                           | 3   | 200         |
| 10                            | 5                             | 10  | 5           |
|                               | 20                            | 10  | 20          |
|                               | 50                            | 10  | 50          |
|                               | 100                           | 10  | 100         |
|                               | 200                           | 10  | 200         |
| 30                            | 5                             | 30  | 5           |
|                               | 20                            | 30  | 20          |
|                               | 50                            | 30  | 50          |
|                               | 100                           | 30  | 100         |
|                               | 200                           | 30  | 200         |

After six weeks, systolic and diastolic blood pressure, left ventricular end diastolic pressure, left ventricular dP/dt, and heart rate are evaluated. The hearts are removed, weighed, measured and fixed in formalin. Collagen content of heart sections are evaluated using computerized image analysis of picrosirius stained sections. It would be expected that rats treated with a combination therapy of AII antagonist and epoxymexrenone components, as compared to rats treated with either component alone, will show improvements in cardiac performance.

TABLE III

In Vivo and In Vitro Angiotensin II  
Activity of Compounds of the Invention

| 5  | Test      | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |            |          |
|----|-----------|----------------------|----------------------|----------------------|------------|----------|
|    | Compound  | IC <sub>50</sub>     | pA <sub>2</sub>      | Dose                 | Inhibition | Duration |
|    | Example # | (nM)                 |                      | (mg/kg)              | (%)        | (min.)   |
| 10 | 1         | NT                   | NT                   | NT                   | NT         | NT       |
|    | 2         | 95                   | 7.37/7.59            | 10                   | 95         | 60       |
|    |           |                      |                      | 30                   | 98         | 90-120   |
|    | 3         | 5.4                  | 8.70 ± 0.2           | 10                   | 50         | >180     |
| 15 |           |                      |                      | 30                   | 100        | 200+     |
|    | 4         | NT                   | NT                   | NT                   | NT         | NT       |
|    | 5         | 200                  | 7.48/6.91            | 30                   | 38         | 20-30    |
|    | 6         | 1300                 | 6.55/6.82            | 100                  | 90         | 120      |
| 20 | 7         | 84                   | 8.01/8.05            | 30                   | 90         | 130      |
|    | 8         | 17,000               | NT                   | NT                   | NT         | NT       |
|    | 9         | 700                  | 6.67/6.12            | 30                   | 80         | 75       |
|    |           |                      |                      | 100                  | 100        | 130      |
| 25 | 10        | 4.9                  | 8.19/7.59            | 3                    | 86         | 100      |
|    |           |                      |                      | 30                   | 100        | 240      |
|    | 11        | 160                  | 6.45/6.77            | NT                   | NT         | NT       |
|    | 12        | 6.0                  | 8.66/8.59            | NT                   | NT         | NT       |
| 30 | 13        | 17                   | 8.70/8.85            | NT                   | NT         | NT       |
|    | 14        | 7.2                  | 8.84/8.71            | NT                   | NT         | NT       |
|    | 15        | 16                   | 8.31/8.30            | NT                   | NT         | NT       |
|    | 16        | 6.4                  | 8.95/9.24            | NT                   | NT         | NT       |
| 30 | 17        | 4.0                  | 8.64/8.40            | NT                   | NT         | NT       |
|    | 18        | 970                  | 6.14/6.09            | NT                   | NT         | NT       |
|    | 19        | 12,000               | 5.18/5.35            | NT                   | NT         | NT       |



| Test | Compound | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |            |          |
|------|----------|----------------------|----------------------|----------------------|------------|----------|
|      |          | IC <sub>50</sub>     | pA <sub>2</sub>      | Dose                 | Inhibition | Duration |
|      |          | Example #            | (nM)                 |                      | (mg/kg)    | (%)      |
| 5    | 20       | 78,000               | 5.89/5.99            | 100                  | 10         | 45       |
|      | 21       | 87                   | 7.71/7.21            | NT                   | NT         | NT       |
|      | 22       | 460                  | 6.60/6.46            | NT                   | NT         | NT       |
|      | 23       | 430                  | 6.48/7.15            | NT                   | NT         | NT       |
|      | 24       | 10                   | 7.56/7.73            | NT                   | NT         | NT       |
| 10   | 25       | 480                  | 6.80/6.73            | NT                   | NT         | NT       |
|      | 26       | 3.2                  | 9.83/9.66            | 10                   | 50         | >180     |
|      | 27       | 180                  | NT                   | NT                   | NT         | NT       |
|      | 28       | 570                  | 5.57/6.00            | NT                   | NT         | NT       |
|      | 29       | 160                  | NT                   | NT                   | NT         | NT       |
| 15   | 30       | 22                   | 7.73/7.88            | 30                   | 50         | >180     |
|      | 31       | 14                   | NT                   | NT                   | NT         | NT       |
|      | 32       | 16                   | 7.68/7.29            | NT                   | NT         | NT       |
|      | 33       | 630                  | 6.73/6.36            | NT                   | NT         | NT       |
|      | 34       | 640                  | 5.34/5.69            | NT                   | NT         | NT       |
| 20   | 35       | 41                   | 7.25/7.47            | NT                   | NT         | NT       |
|      | 36       | 1400                 | 5.92/5.68            | NT                   | NT         | NT       |
|      | 37       | 340                  | 6.90/6.85            | NT                   | NT         | NT       |
|      | 38       | 10                   | 7.82/8.36            | NT                   | NT         | NT       |
|      | 39       | 10                   | 7.88/7.84            | NT                   | NT         | NT       |
| 25   | 40       | 83                   | 7.94/7.61            | NT                   | NT         | NT       |
|      | 41       | 3700                 | 5.68/5.96            | NT                   | NT         | NT       |
|      | 42       | 370                  | 6.56/6.26            | NT                   | NT         | NT       |
|      | 43       | 19                   | 8.97/8.61            | NT                   | NT         | NT       |
|      | 44       | 16                   | 8.23/7.70            | NT                   | NT         | NT       |
| 30   | 45       | 4.4                  | 8.41/8.24            | NT                   | NT         | NT       |
|      | 46       | 110                  | 6.80/6.64            | NT                   | NT         | NT       |

| T st | Compound | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |            |          |
|------|----------|----------------------|----------------------|----------------------|------------|----------|
|      |          | IC <sub>50</sub>     | pA <sub>2</sub>      | Dos                  | Inhibition | Duration |
|      |          | (nM)                 |                      | (mg/kg)              | (%)        | (min.)   |
| 5    | 47       | 21                   | 7.85/7.58            | NT                   | NT         | NT       |
|      | 48       | 680                  | 6.27/6.75            | NT                   | NT         | NT       |
|      | 49       | 120                  | 7.06/7.07            | NT                   | NT         | NT       |
|      | 50       | 54                   | 7.71/7.89            | NT                   | NT         | NT       |
|      | 51       | 8.7                  | 8.39/8.51            | NT                   | NT         | NT       |
| 10   | 52       | 100                  | 8.14/8.12            | NT                   | NT         | NT       |
|      | 53       | 65                   | 7.56/7.83            | NT                   | NT         | NT       |
|      | 54       | 3100                 | 6.02                 | NT                   | NT         | NT       |
|      | 55       | 80                   | 6.56/7.13            | NT                   | NT         | NT       |
|      | 56       | 5.0                  | 9.04/8.35            | NT                   | NT         | NT       |
| 15   | 57       | 2300                 | 6.00                 | NT                   | NT         | NT       |
|      | 58       | 140                  | 6.45/6.57            | NT                   | NT         | NT       |
|      | 59       | 120                  | 7.23/7.59            | NT                   | NT         | NT       |
|      | 60       | 2200                 | 6.40/6.03            | NT                   | NT         | NT       |
|      | 61       | 110                  | 7.29/7.70            | NT                   | NT         | NT       |
| 20   | 62       | 26                   | 8.69/8.61            | NT                   | NT         | NT       |
|      | 63       | 61                   | 7.77/7.67            | NT                   | NT         | NT       |
|      | 64       | 54                   | 7.00/6.77            | NT                   | NT         | NT       |
|      | 65       | 23                   | 7.85/7.75            | NT                   | NT         | NT       |
|      | 66       | 12                   | 9.34/8.58            | NT                   | NT         | NT       |
| 25   | 67       | 3100                 | 5.88/5.78            | NT                   | NT         | NT       |
|      | 68       | 8.6                  | 8.19/8.65            | NT                   | NT         | NT       |
|      | 69       | 15                   | 7.80/8.28            | NT                   | NT         | NT       |
|      | 70       | 44                   | 7.71/8.05            | NT                   | NT         | NT       |
|      | 71       | 12,000               | *                    | NT                   | NT         | NT       |
| 30   | 72       | 83                   | 6.11/6.10            | NT                   | NT         | NT       |
|      | 73       | 790                  | 7.65/7.46            | NT                   | NT         | NT       |

| T st      | Compound | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |            |          |
|-----------|----------|----------------------|----------------------|----------------------|------------|----------|
|           |          | IC <sub>50</sub>     | pA <sub>2</sub>      | Dose                 | Inhibition | Duration |
| Example # |          | (nM)                 |                      | (mg/kg)              | (%)        | (min.)   |
| 5         | 74       | 6.5                  | 8.56/8.39            | NT                   | NT         | NT       |
|           | 75       | 570                  | 6.00/5.45            | NT                   | NT         | NT       |
|           | 76       | 5400                 | 5.52/5.78            | NT                   | NT         | NT       |
|           | 77       | 15,000               | 5.77                 | NT                   | NT         | NT       |
|           | 78       | 101                  | 7.0                  |                      | 93         | 60-100   |
| 10        | 79       | 4.9                  | 9.2                  |                      | 100        | >200     |
|           |          |                      |                      |                      | 50         | >180     |
|           | 80       | 25                   | 8.1                  |                      | NT         | NT       |
|           | 81       | 18                   | 8.0                  |                      | 40         | 180      |
|           | 82       | 7.9                  | 8.5                  |                      | 20         | 180      |
| 15        | 83       | 3.6                  | 8.3                  |                      | 15         | >180     |
|           | 84       | 16                   | 7.1                  |                      | 20         | 30       |
|           | 85       | 8.7                  | 8.9                  |                      | NT         | NT       |
|           | 86       | 9                    | 7.8                  |                      | NT         | NT       |
|           | 87       | 91                   | 7.8                  |                      | NT         | NT       |
| 20        | 88       | 50                   | 7.7                  |                      | NT         | NT       |
|           | 89       | 18                   | 7.9                  |                      | NT         | NT       |
|           | 90       | 5.6                  | 9.0                  |                      | NT         | NT       |
|           | 91       | 30                   | 8.6                  |                      | 40         | >180     |
|           | 92       | 35                   | 7.9                  |                      | NT         | NT       |
| 25        | 93       | 480                  | NT                   |                      | NT         | NT       |
|           | 94       | 5,800                | NT                   |                      | NT         | NT       |
|           | 95       | 66                   | 8.2                  |                      | NT         | NT       |
|           | 96       | 21                   | 8.0                  |                      | NT         | NT       |
|           | 97       | 280                  | 7.7                  |                      | NT         | NT       |
| 30        | 98       | 22                   | 8.1                  |                      | NT         | NT       |
|           | 99       | 280                  | 6.5                  |                      | NT         | NT       |
|           | 100      | 4.4                  | 9.4                  |                      | NT         | NT       |
|           | 101      | 36                   | 7.8                  |                      | NT         | NT       |

| T st      | 1Assay A         | 2Assay B        | 3Assay C  |            |          |      |
|-----------|------------------|-----------------|-----------|------------|----------|------|
| Compound  | IC <sub>50</sub> | pA <sub>2</sub> | Dose      | Inhibition | Duration |      |
| Example # | (nM)             |                 | (mg/kg)   | (%)        | (min.)   |      |
| 5         | 102              | 43              | 7.7       | NT         | NT       |      |
|           | 103              | 12              | 8.0       | NT         | NT       |      |
|           | 104              | 15              | 8.0       | NT         | NT       |      |
|           | 105              | 290             | 6.6       | NT         | NT       |      |
|           | 106              | 48              | 7.7       | NT         | NT       |      |
| 10        | 107              | 180             | 8.3       | NT         | NT       |      |
|           | 108              | 720             | 5.3       | 100        | 45       | 90   |
|           | 109              | 250             | 7.3       | 30         | 50       | 30   |
|           | 110              | 590             | 6.4       |            | NT       | NT   |
|           | 111              | 45              | 9.0       | 30         | 87       | 160  |
| 15        | 112              | 2000            | 5.2       |            | NT       | NT   |
|           | 113              | 12              | 8.4       | 10         | 60       | 180  |
|           | 114              | 400             | 6.4       |            | NT       |      |
|           | 115              | 11              | 8.2       | 3          | 40       | >240 |
|           | 116              | 230             | 6.5       |            | NT       |      |
| 20        | 117              | 170             | 6.5       |            | NT       |      |
|           | 118              | 37              | 9.21/9.17 | 10         | 70       | 120  |
|           | 119              | 16              | 9.21/9.00 | 3          | 20       | 60   |
|           | 120              | 25              | 9.05/8.77 | 10         | 80       | 240  |
|           | 121              | 46              | NT        |            | NT       |      |
| 25        | 122              | 46              | NT        |            | NT       |      |
|           | 123              | 50              | NT        |            | NT       |      |
|           | 124              | 40              | 9.42/9.12 | 3          | 45       | >180 |
|           | 125              | 40              | 9.25/8.80 | 3          | 35       | >240 |

| Test      | Compound | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |            |
|-----------|----------|----------------------|----------------------|----------------------|------------|
|           |          | IC <sub>50</sub>     | pA <sub>2</sub>      | Dose                 | Inhibition |
| Example # |          | (nM)                 |                      | (mg/kg)              | (%)        |
| 5         | 126      | 240                  | 7.20/7.05            |                      | NT         |
|           | 127      | 12,000               | 4.96                 |                      | NT         |
|           | 128      | 16                   | 8.63/8.40            |                      | NT         |
|           | 129      | 6,700                | 5.30                 |                      | NT         |
|           | 130      | 40                   | 8.10/7.94            |                      | NT         |
| 10        | 131      | 9.5                  | 7.53/8.25            |                      |            |
|           | 132      | 12                   | 8.6                  |                      | NT         |
|           | 133      | 10                   | 8.7                  | 3                    | 20         |
|           |          |                      |                      |                      | 180        |
|           |          |                      |                      |                      | 90-120     |
|           | 134      | 22                   | 9.3                  | 3                    | 35         |
| 15        | 135      | 16                   | 8.5                  | 3                    | 35         |
|           | 136      | NT                   | NT                   |                      | NT         |
|           | 137      | 220                  | 8.3                  |                      | NT         |
|           | 138      | 130                  | 8.2                  |                      | NT         |
|           | 139      | 0.270                | 6.3                  |                      | NT         |
| 20        | 140      | 0.031                | 8.1                  |                      | 100        |
|           | 141      | 0.110                | 8.02                 |                      | NT         |
|           | 142      | 2.000                | NA                   |                      | NT         |
|           | 143      | 0.052                | 7.7                  |                      | 85         |
|           | 144      | 0.088                | 7.7                  |                      | 50         |
| 25        | 145      | 0.480                | 6.7                  |                      | NT         |
|           | 146      | 0.072                | 6.4                  |                      | NT         |

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| Test      |     | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |            |          |
|-----------|-----|----------------------|----------------------|----------------------|------------|----------|
| Compound  |     | IC <sub>50</sub>     | pA <sub>2</sub>      | Dose                 | Inhibition | Duration |
| Example # |     | (nM)                 |                      | (mg/kg)              | (%)        | (min.)   |
| 5         | 147 | 5.8                  | 5.6                  | 3                    | 74         | 5-10     |
|           | 148 | 0.87                 | 5.8                  | 3                    | 92         | 20-30    |
|           | 149 | 1.1                  | 6.1                  | 3                    | NT         | NT       |
|           | 150 | 14                   | 8.03/7.80            | 3                    | 25         | >180     |
|           | 151 | 17                   | 7.76/7.97            | 3                    | 15         | 180      |
| 10        | 152 | 150                  | 7.46/7.23            | 3                    | 10         | 140      |
|           | 153 | 13                   | 8.30/7.69            | 3                    | 25         | >180     |
|           | 154 | 97                   | 8.19/8.38            |                      | NA         |          |
|           | 155 | 86                   | 7.60/7.14            |                      | NA         |          |
|           | 156 | 78                   | 8.03/7.66            |                      | NA         |          |
| 15        | 157 | 530                  | - /6.22              |                      | NA         |          |
|           | 158 | 54                   | 8.23/8.14            | 3                    | 30         | >180     |
|           | 159 | 21                   | 7.92/7.56            | 3                    | 10         | 150      |
|           | 160 | 64                   | 7.87/7.71            |                      |            |          |
|           | 161 | 28                   |                      |                      | NA         |          |
| 20        | 162 | 380                  | 6.21/6.55            |                      | NA         |          |
|           | 163 | 420                  | 7.42/6.75            |                      | NA         |          |
|           | 164 | 1700                 |                      |                      | NA         |          |
|           | 165 | 410                  | 6.90/7.18            |                      | NA         |          |

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| Test      | Compound | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |          |
|-----------|----------|----------------------|----------------------|----------------------|----------|
|           |          | IC <sub>50</sub>     | pA <sub>2</sub>      | Inhibition           | Duration |
| Example # |          | (nM)                 |                      | (%)                  | (min.)   |
| 5         | 166      | 160                  | 7.57/7.74            |                      | NA       |
|           | 167      | 370                  | 7.08/7.11            |                      | NA       |
|           | 168      | 420                  | 7.69/7.58            |                      | NA       |
|           | 169      | 150                  | 7.78/7.58            | 3                    | 15       |
|           | 170      | 26                   | 7.08/7.77            | 3                    | 40       |
| 10        | 171      | 28                   | 7.52/7.11            | 3                    | 0        |
|           | 172      | 70                   | 7.15/7.04            |                      | NA       |
|           | 173      | 90                   | 7.49/6.92            |                      | NA       |
|           | 174      | 180                  | 7.29/7.02            |                      | NA       |
|           | 175      | 27                   | NA                   | 3                    | 0        |
| 15        | 176      | 9.8                  | 7.69/7.55            | 3                    | 10       |
|           | 177      | 26                   | 7.41/7.85            | 3                    | 15       |
|           | 178      | 88                   | 7.54/7.47            |                      | NA       |
|           | 179      | 310                  | 6.67/ -              |                      | NA       |
|           | 180      | 20                   | 7.56/7.15            | 3                    | 25       |
| 20        | 181      | 21                   | 7.70/7.12            | 3                    | 20       |
|           | 182      | 59                   | NA                   |                      | NA       |
|           | 183      | 390                  | NA                   |                      | NA       |
|           | 184      | 1100                 | 6.78/ -              |                      | NA       |

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| Test      | Compound | <sup>1</sup> Assay A | <sup>2</sup> Assay B | Dose    | <sup>3</sup> Assay C |          |
|-----------|----------|----------------------|----------------------|---------|----------------------|----------|
|           |          | IC <sub>50</sub>     | pA <sub>2</sub>      |         | Inhibition           | Duration |
| Example # |          | (nM)                 |                      | (mg/kg) | (%)                  | (min.)   |
| 5         | 185      | 6.5                  | 8.82/8.53            | 3       | 50                   | > 180    |
|           | 186      | 38                   | 8.13/7.40            | 3       | 25                   | 180      |
|           | 187      | 770                  | 7.46/6.95            |         | NA                   |          |
|           | 188      | 140                  | 7.72/7.09            |         | NA                   |          |
|           | 189      | 29                   | 8.64/8.23            |         | NA                   |          |
| 10        | 190      | 10                   | 7.87/7.89            | 3       | 10                   | 180      |
|           | 191      | 81                   | 7.75/7.76            | 3       | 10                   | 180      |
|           | 192      | 140                  |                      |         | NA                   |          |
|           | 193      | 11                   | 9.27/8.87            | 3       | 10                   | 180      |
|           | 194      | 47                   | 7.64/7.35            |         | NA                   |          |
| 15        | 195      | 34                   | 8.44/8.03            |         | NA                   |          |
|           | 196      | 31                   | 7.68/8.26            |         | NA                   |          |
|           | 197      | 14                   | 8.03/8.60            |         | NA                   |          |
|           | 198      | 7.6                  | 8.76/8.64            | 3       | 35                   | > 180    |
|           | 199      | 10                   | 8.79/8.85            | 3       | 60                   | > 180    |
| 20        | 200      | 20                   | 8.42/8.77            | 3       | 45                   | > 180    |
|           | 201      | 17                   | 8.78/8.63            | 3       | 10                   | 180      |
|           | 202      | 12                   | 8.79/8.64            | 3       | 65                   | > 180    |
|           | 203      | 9.2                  | 8.43/8.36            | 3       | 50                   | > 180    |
|           | 204      | 16                   | 9.17/8.86            | 3       | 75                   | > 180    |
| 25        | 205      | 20                   | 9.14/9.15            | 3       | 40                   | > 180    |
|           | 206      | 5.4                  | 8.75/8.89            | 3       | 30                   | > 180    |
|           | 207      | 99                   | 9.04/8.60            |         | NA                   |          |
|           | 208      | 22                   | 9.19/8.69            | 3       | 50                   | > 180    |
|           | 209      | 5.0                  | 9.41/9.16            | 3       | 25                   | > 180    |
| 30        | 210      | 3.6                  | 8.36/8.44            | 3       | 15                   | 180      |
|           | 211      | 18                   | 8.74/8.67            | 3       | 35                   | > 180    |
|           | 212      | 23                   | 8.85/8.25            | 3       | 15                   | 180      |
|           | 213      | 51                   | NA                   |         | NA                   |          |
|           | 214      | 65                   | NA                   |         | NA                   |          |
| 35        | 215      | 45                   | NA                   |         | NA                   |          |
|           | 216      | 5.4                  | 8.80/9.04            | 3       | 50                   | > 180    |



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| Test      | <sup>1</sup> Assay A | <sup>2</sup> Assay B | <sup>3</sup> Assay C |            |          |       |
|-----------|----------------------|----------------------|----------------------|------------|----------|-------|
| Compound  | IC <sub>50</sub>     | pA <sub>2</sub>      | Dose                 | Inhibition | Duration |       |
| Example # | (nM)                 |                      | (mg/kg)              | (%)        | (min.)   |       |
| 5         |                      |                      |                      |            |          |       |
|           | 217                  | 9.4                  | NA                   | 3          | 65       | > 180 |
|           | 218                  | 9.0                  | NA                   |            | NA       |       |
|           | 219                  | 14                   | NA                   |            | NA       |       |
|           | 220                  | 7.0                  | NA                   | 3          | 75       | 120   |
| 10        | 221                  | 4.8                  | NA                   | 3          | 25       | > 180 |
|           | 222                  | 5.0                  | NA                   |            | NA       |       |
|           | 223                  | 14                   | 7.45/7.87            | 3          | 20       | > 180 |
|           | 224                  | 91                   | NA                   |            | NA       |       |
|           | 225                  | 160                  | NA                   |            | NA       |       |
| 15        | 226                  | 93                   | NA                   |            | NA       |       |
|           | 227                  | 89                   | 7.55/7.67            |            | NA       |       |
|           | 228                  | 4.5                  | 9.17/8.25            | 3          | 80       | >180  |
|           | 229                  | 19                   | NT                   | 3          | 40       | >180  |
|           | 230                  | 2.6                  | 8.23/8.69            | 3          | 25       | >180  |
| 20        | 231                  | 3.6                  | NT                   | 3          | 75       | >180  |
|           | 232                  | 4.4                  | 8.59/8.89            | 3          | 70       | >180  |
|           | 233                  | 84                   | 8.51/8.78            |            | NT       |       |
|           | 234                  | 5.0                  | 8.49/9.00            | 3          | 20       | -     |
|           | 235                  | 34                   | 7.14/7.07            |            | NT       |       |
| 25        | 236                  | 4.9                  | NC                   | 3          | 70       | >180  |
|           | 237                  | 3.6                  | NT                   |            | NT       |       |
|           | 238                  | 1.7                  | NT                   | 3          | 15       | >180  |
|           | 239                  | 6.8                  | 7.88/8.01            | 3          | 20       | >180  |
|           | 240                  | 120                  | NA                   |            | NA       |       |
| 30        | 241                  | 6.9                  | 8.57/8.24            | 3          | 40       | >180  |
|           | 242                  | 110                  | 7.11/6.60            |            | NA       |       |
|           | 243                  | 250                  | NA                   |            | NA       |       |
|           | 244                  | 150                  | 7.17/7.17            |            | NA       |       |
|           | 245                  | 98                   | 6.64/7.04            |            | NA       |       |
| 35        | 246                  | 72                   | 7.46/7.59            |            | NA       |       |
|           | 247                  | 9.4                  | 8.26/8.41            | 3          | 20       | 180   |

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| Test      | <sup>1</sup> Assay A |                  | <sup>2</sup> Assay B |         | <sup>3</sup> Assay C |           |
|-----------|----------------------|------------------|----------------------|---------|----------------------|-----------|
|           | Compound             | IC <sub>50</sub> | pA <sub>2</sub>      | Dose    | Inhibition           | Duration  |
| Example # |                      | (nM)             |                      | (mg/kg) | (%)                  | (min.)    |
| 5         | 248                  | 20               | 7.68/7.50            | 3       | 10                   | --        |
|           | 249                  | 4.4              | NA                   | 3       | 20                   | >180      |
|           | 250                  | 43               | NA                   | 3       | 0                    | --        |
|           | 251                  | 25               | NA                   |         | NA                   |           |
|           | 252                  | 13               | NA                   |         | NA                   |           |
| 10        | 253                  | 2.6              | NA                   |         | NA                   |           |
|           | 254                  | 72               | NA                   |         | NA                   |           |
|           | 255                  | 12               | 7.61/7.46            | 3       | 20                   | >180      |
|           | 256                  | 4.1              | 8.43/7.78            | 3       | 30                   | >180      |
|           | 257                  | 160              | 6.63/6.68            |         | NA                   |           |
| 15        | 258                  | 350              | 6.84/6.84            |         | NA                   |           |
|           | 259                  | 54               | NA                   |         | NA                   |           |
|           | 260                  | 220              | NA                   |         | NA                   |           |
|           | 261                  | 18               | NA                   |         | NA                   |           |
|           | 262                  | 530              | -/6.22               |         | NA                   |           |
| 20        | 263                  | 57               | NA                   |         | NA                   |           |
|           | 264                  | 11               | NA                   |         | NA                   |           |
|           | 265                  | 110              | NA                   |         | NA                   |           |
|           | 266                  | 290              | NA                   |         | NA                   |           |
|           | 267                  | 25               | NA                   | 3       | 25                   | >180      |
| 25        | 268                  | 520              | NA                   | 3       | 0                    | --        |
|           | 269                  | 9.7              | NA                   |         | NA                   |           |
|           | 270                  | 21               | NA                   |         | NA                   |           |
|           | 271                  | 14               | NC                   | 3       | 20%                  | --        |
|           | 272                  | 97               | NC                   | 3       | 70%                  | >180 min. |
| 30        | 273                  | 9.8              | 8.53/8.61            | 3       | 25%                  | >180 min. |
|           | 274                  | 13               | 9.06/8.85            | 3       | 35%                  | >180 min. |
|           | 275                  | 6.3              | 9.07/ --             | 3       | 40%                  | >180 min. |
|           | 276                  | 33               | 8.71/8.64            | 3       | <20%                 |           |
|           | 277                  | 190              | -- /6.54             |         | NT                   |           |
| 35        | 278                  | 30               | 8.49/8.51            | 3       | 50%                  | >180 min. |
|           | 279                  | 270              | 8.06/8.25            |         | NT                   |           |
|           | 280                  | 480              | 6.41/6.35            | NT      | NT                   | NT        |

NT = NOT TESTED

NC = Non-Competitive antagonist

5     \*Antagonist Activity not observed up to 10  $\mu$ M of test  
      compound.

1Assay A: Angiotensin II Binding Activity

2Assay B: In Vitro Vascular Smooth Muscle Response

3Assay C: In Vivo Pressor Response

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Test Compounds administered intragastrically, except for  
compounds of examples #1-#2, #4-#25, #27-#29, #30-#79,  
#108-#109, #111, #118 and #139-#149 which were given  
intraduodenally.

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Administration of the angiotensin II receptor antagonist and the aldosterone receptor antagonist may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropyl-methyl cellulose, together with one or more of a lubricant, preservative, surface-active or dispersing agent.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of each active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.01 to 30 mg/kg body weight, particularly from about 1 to 15 mg/kg body weight, may be appropriate.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose of each active component is from about 0.01 to 15 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred

daily dose would be from about 1 to 10 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 15 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 15 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 10 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

In combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 5 mg to about 400 mg, and the AII antagonist may be present in an amount in a range from about 1 mg to about 800 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 400:1 to about 1:160.

In a preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 10 mg to about 200 mg, and the AII antagonist may be present in an amount in a range from about 5 mg to about 600 mg, which represents aldosterone antagonist-to-AII antagonist ratios ranging from about 40:1 to about 1:60.

In a more preferred combination therapy, the aldosterone receptor antagonist may be present in an amount in a range from about 20 mg to about 100 mg, and the AII antagonist may be present in an amount in a range from about 10 mg to about 400 mg, which represents aldosterone

antagonist-to-AII antagonist ratios ranging from about 10:1 to about 1:20.

The dosage regimen for treating a disease condition with the combination therapy of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the active components of this combination therapy invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the components may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The components may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What Is Claimed Is:

1. A combination comprising a therapeutically-effective amount of an angiotensin II receptor antagonist  
5 and a therapeutically-effective amount of an epoxy-steroidal aldosterone receptor antagonist.
2. The combination of Claim 1 wherein said epoxy-steroidal aldosterone receptor antagonist is  
10 selected from epoxy-containing compounds.
3. The combination of Claim 2 wherein said epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroidal nucleus of a 20-spiroxane  
15 compound.
4. The combination of Claim 3 wherein said 20-spiroxane compound is characterized by the presence of a 9 $\alpha$ -,11 $\alpha$ -substituted epoxy moiety.  
20
5. The combination of Claim 2 wherein said epoxy-containing compound is selected from the group consisting of  
25 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, $\gamma$ -lactone, methyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;  
pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;  
30 3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ -lactone, (6 $\beta$ ,7 $\beta$ ,11 $\beta$ ,17 $\beta$ )-;  
35 pregn-4-ene-7,21-dicarboxylic acid,9,11-epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester, monopotassium salt, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;



pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

5

3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,  $\gamma$ -lactone (6 $\alpha$ ,7 $\alpha$ ,11. $\alpha$ )-;

10 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

15 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

20 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,  $\gamma$ -lactone, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,  $\gamma$ -lactone, ethyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-; and

25

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,  $\gamma$ -lactone, 1-methylethyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-.

30

6. The combination of Claim 1 wherein said angiotensin II receptor antagonist is selected from compounds consisting of a first portion and a second portion, wherein said first portion is selected from a fragment of Formula I:

- Ar-Alk-L  
Ar-L-Ar-Alk-L  
Het-L-Ar-Alk-L  
5 Het-L-Het-Alk-L (I)  
Ar-L-Het-Alk-L  
Het-L-Alk-L

wherein Ar is a five or six-membered  
10 carbocyclic ring system consisting of one ring or two  
fused rings, with such ring or rings being fully  
unsaturated or partially or fully saturated;

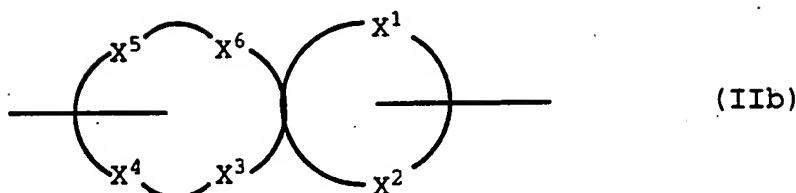
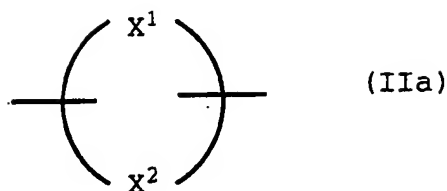
wherein Het is a monocyclic or bicyclic fused  
15 ring system having from five to eleven ring members, and  
having at least one of such ring members being a hetero  
atom selected from one or more hetero atoms selected from  
oxygen, nitrogen and sulfur, and with such ring system  
containing up to six of such hetero atoms as ring  
20 members;

wherein Alk is an alkyl radical or alkylene  
chain; linear or branched, containing from one to about  
five carbon atoms;

25 wherein L is a straight bond or a bivalent  
linker moiety selected from carbon, oxygen and sulfur;

and wherein said second portion is a monocyclic  
30 heterocyclic moiety selected from moieties of Formula IIa  
or is a bicyclic heterocyclic moiety selected from  
moieties of Formula IIb:

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wherein each of X<sup>1</sup> through X<sup>6</sup> is selected from -CH=, -CH<sub>2</sub>-, -N=, -NH-, O, and S, with the proviso that at least one of X<sup>1</sup> through X<sup>6</sup> in each of Formula IIa and Formula IIb must be a hetero atom, and wherein said heterocyclic moiety of Formula IIa or IIb may be attached through a bond from any ring member of the Formula IIa or IIb heterocyclic moiety having a substitutable or a bond-forming position.

7. The combination of Claim 6 wherein said monocyclic heterocyclic moiety of Formula IIa is selected from thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl, 1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

8. The combination of Claim 7 wherein said bicyclic heterocyclic moiety of Formula IIb is selected from benzo[b]thienyl, isobenzofuranyl, chromenyl, indoliziny, isoindolyl, indolyl, indazolyl, purinyl, quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiololo-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

9. The combination of Claim 8 wherein said angiotensin II receptor antagonist compound having said first-and-second-portion moieties of Formula I and II is further characterized by having an acidic moiety attached to either of said first-and-second-portion moieties.

10. The combination of Claim 9 wherein said acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

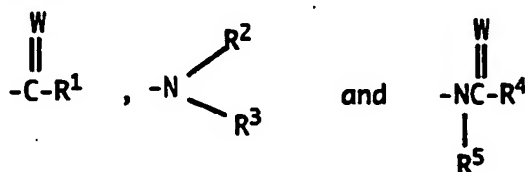


wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide,

ester and salt derivatives of said acidic moieties;  
 wherein U is a spacer group independently selected from  
 one or more of alkyl, cycloalkyl, cycloalkylalkyl,  
 alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one  
 5 or more ring atoms selected from oxygen, sulfur and  
 nitrogen atoms.

11. The combination of Claim 10 wherein said  
 acidic moiety is selected from carboxyl moiety and  
 10 tetrazolyl moiety.

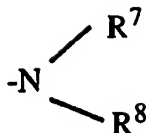
12. The combination of Claim 10 wherein any of  
 the moieties of Formula I and Formula II may be  
 substituted at any substitutable position by one or more  
 15 radicals selected from hydrido, hydroxy, alkyl, alkenyl,  
 alkynyl, aralkyl, hydroxyalkyl, haloalkyl, halo, oxo,  
 alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl,  
 cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl,  
 cyano, cyanoamino, nitro, alkylcarbonyloxy,  
 20 alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl,  
 aralkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl,  
 alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl,  
 alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl,  
 aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl  
 25 having one or more ring atoms selected from oxygen,  
 sulfur and nitrogen atoms, and amino and amido radicals  
 of the formula



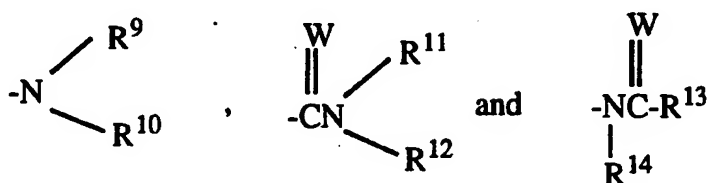
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wherein W is oxygen atom or sulfur atom; wherein each of  
 R<sup>1</sup> through R<sup>5</sup> is independently selected from hydrido,  
 alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR<sup>6</sup>  
 and

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wherein Y is selected from oxygen atom and sulfur atom and R<sup>6</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is further independently selected from amino and amido radicals of the formula



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wherein W is oxygen atom or sulfur atom; wherein each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>2</sup> and R<sup>3</sup> taken together and each of R<sup>4</sup> and R<sup>5</sup> taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of R<sup>2</sup> and R<sup>3</sup> taken together and each of R<sup>7</sup> and R<sup>8</sup> taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido

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radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

5

13. The combination of Claim 12 wherein said angiotensin II receptor antagonist is 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor antagonist is 9 $\alpha$ -, 11 $\alpha$ -epoxy-7 $\alpha$ -methoxycarbonyl-20-spirox-4-ene-3,21-dione or a pharmaceutically-acceptable salt thereof.

10  
15

14. The combination of Claim 13 further characterized by said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about twenty-to-one of said angiotensin II receptor antagonist to said aldosterone receptor antagonist.

20

15. The combination of Claim 14 wherein said weight ratio range is from about five-to-one to about fifteen-to-one.

25

16. The combination of Claim 15 wherein said weight ratio range is about ten-to-one.

30

17. The combination of Claim 1 wherein said angiotensin II receptor antagonist is selected from the group consisting of: saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22,

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WAY-126227, WK-1492.2K, YM-31472, losartan potassium,  
E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,  
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,  
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,  
5 L-162441, L-163007, PD-123177, A-81988, BMS-180560,  
CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167,  
EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739,  
HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline,  
KRI-1177, L-158809, L-158978, L-159874, LR B087,  
10 LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970,  
RWJ-46458, S-8307, S-8308, saprisartan, saralasin,  
Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731,  
BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017,  
LY-301875, XH-148, XR-510, zolasartan and PD-123319.

15

18. The combination of Claim 17 wherein said  
angiotensin II receptor antagonist is selected from the  
group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170,  
20 EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,  
BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,  
EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,  
LY-235656, PD-150304, U-96849, U-97018, UP-275-22,  
WAY-126227, WK-1492.2K, YM-31472, losartan potassium,  
25 E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,  
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,  
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,  
L-162441, L-163007 and PD-123177.

30

19. A co-therapy for treating cardiovascular  
disorders in a subject afflicted with or susceptible to  
multiple cardiovascular disorders, wherein said co-  
therapy comprises administering a therapeutically-  
effective amount of an angiotensin II receptor antagonist  
35 and administering a therapeutically effective amount of  
an epoxy-steroidal aldosterone receptor antagonist.



20. The co-therapy of Claim 19 wherein said subject is afflicted with or susceptible to or afflicted with hypertension.

5 21. The co-therapy of Claim 19 wherein said subject is susceptible to or afflicted with congestive heart failure.

10 22. The co-therapy of Claim 19 further characterized by administering said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist in a sequential manner.

15 23. The co-therapy of Claim 19 further characterized by administering said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist in a substantially simultaneous manner.

20 24. The co-therapy of Claim 19 wherein said angiotensin II receptor antagonist is 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor  
25 antagonist is  
9 $\alpha$ -, 11 $\alpha$ -epoxy-7 $\alpha$ -methoxycarbonyl-20-spirox-4-ene-3, 21-dione or a pharmaceutically-acceptable salt thereof.

30 25. The co-therapy of Claim 24 further characterized in administering said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist is a weight ratio range from about two-to-one to about fifty-to-one of said angiotensin II  
35 receptor antagonist to said aldosterone receptor antagonist.

26. The co-therapy of Claim 25 wherein said

weight ratio range is from about two-to-one to about ten-to-one.

27. The co-therapy of Claim 26 wherein said  
5 weight ratio range is about five-to-one.

28. A method to treat a subject susceptible to  
or afflicted with congestive heart failure, which method  
10 comprises administering a combination of drug agents  
comprising a therapeutically-effective amount of an  
angiotensin II receptor antagonist and a therapeutically-  
effective amount of an epoxy-steroidal aldosterone  
receptor antagonist.

15

29. The method of Claim 28 wherein said epoxy-  
steroidal aldosterone receptor antagonist is selected  
from epoxy-containing compounds.

20

30. The method of Claim 29 wherein said epoxy-  
containing compound has an epoxy moiety fused to the "C"  
ring of the steroidal nucleus of a 20-spiroxane compound.

31. The method of Claim 30 wherein said 20-  
25 spiroxane compound is characterized by the presence of a  
9 $\alpha$ -,11 $\alpha$ -substituted epoxy moiety.

32. The method of Claim 29 wherein said epoxy-  
containing compound is selected from the group consisting  
30 of

pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-  
17-hydroxy-3-oxo, $\gamma$ -lactone, methyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

35 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-  
17-hydroxy-3-oxo-dimethyl ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid,  
9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ -  
lactone, (6 $\beta$ ,7 $\beta$ ,11 $\beta$ ,17 $\beta$ )-;

- 5 pregn-4-ene-7,21-dicarboxylic acid,9,11-  
epoxy-17-hydroxy-3-oxo-,7-(1-methylethyl) ester,  
monopotassium salt, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

- 10 pregn-4-ene-7,21-dicarboxylic acid,9,11,-epoxy-  
17-hydroxy-3-oxo-,7-methyl ester, monopotassium  
salt, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

- 15 3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-  
carboxylic acid, 9,11-epoxy-6,7-dihydro-17-  
hydroxy-3-oxo-, $\gamma$ -lactone(6 $\alpha$ ,7 $\alpha$ ,11. $\alpha$ )-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic  
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,  
methyl ester, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

- 20 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic  
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,  
monopotassium salt, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-;

- 25 3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic  
acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, $\gamma$ -  
lactone, (6 $\alpha$ ,7 $\alpha$ ,11 $\alpha$ .,17 $\alpha$ )-;

- 30 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-  
17-hydroxy-3-oxo-, $\gamma$ -lactone, ethyl ester,  
(7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-; and

- 35 pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-  
17-hydroxy-3-oxo-, $\gamma$ -lactone, 1-methylethyl  
ester, (7 $\alpha$ ,11 $\alpha$ ,17 $\alpha$ )-.

33. The method of Claim 28 wherein said  
angiotensin II receptor antagonist is selected from

compounds consisting of a first portion and a second portion, wherein said first portion is selected from a fragment of Formula I:

- 5                   Ar-Alk-L  
                  Ar-L-Ar-Alk-L  
                  Het-L-Ar-Alk-L  
                  Het-L-Het-Alk-L                   (I)  
                  Ar-L-Het-Alk-L  
10                  Het-L-Alk-L

                  wherein Ar is a five or six-membered carbocyclic ring system consisting of one ring or two fused rings, with such ring or rings being fully  
15   unsaturated or partially or fully saturated;

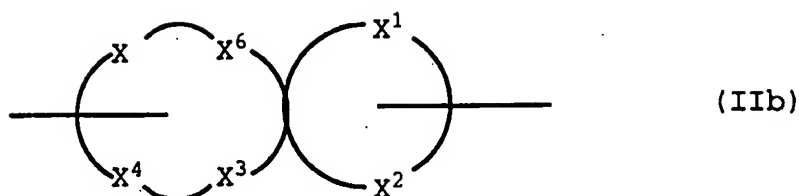
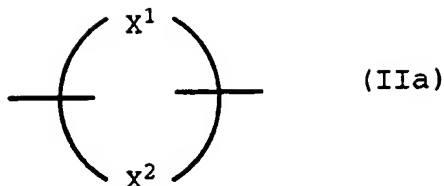
                  wherein Het is a monocyclic or bicyclic fused ring system having from five to eleven ring members, and having at least one of such ring members being a hetero  
20   atom selected from one or more hetero atoms selected from oxygen, nitrogen and sulfur, and with such ring system containing up to six of such hetero atoms as ring members;

25                  wherein Alk is an alkyl radical or alkylene chain, linear or branched, containing from one to about five carbon atoms;

                  wherein L is a straight bond or a bivalent  
30   linker moiety selected from carbon, oxygen and sulfur;

                  and wherein said second portion is a monocyclic heterocyclic moiety selected from moieties of Formula IIa or is a bicyclic heterocyclic moiety selected from  
35   moieties of Formula IIb:

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wherein each of X<sup>1</sup> through X<sup>6</sup> is selected from -CH=, -CH<sub>2</sub>-, -N=, -NH-, O, and S, with the proviso that at least one of X<sup>1</sup> through X<sup>6</sup> in each of Formula IIa and Formula IIb must be a hetero atom, and wherein said heterocyclic moiety of Formula IIa or IIb may be attached through a bond from any ring member of the Formula IIa or IIb heterocyclic moiety having a substitutable or a bond-forming position.

34. The method of Claim 33 wherein said monocyclic heterocyclic moiety of Formula IIa is selected from thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, triazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isothiazolyl, isoxazolyl, furazanyl, pyrrolidinyl, pyrrolinyl, furanyl, thiophenyl, isopyrrolyl, 3-isopyrrolyl, 2-isoimidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, oxazolyl, thiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, 1,2-pyronyl, 1,4-pyronyl, pyridinyl, piperazinyl, s-triazinyl, as-triazinyl, v-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,3,6-

oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl, 1,3,5,2-oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

35. The method of Claim 34 wherein said bicyclic heterocyclic moiety of Formula IIb is selected from benzo[b]thienyl, isobenzofuranyl, chromenyl, indolizinyll, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyll, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyll, quinazolinyl, cinnolinyl, pteridinyl isochromanyl, chromanyl, thieno[2,3-b]furanyl, 2H-furo[3,2-b]pyranyl, 5H-pyrido[2,3-d][1,2]oxazinyl, 1H-pyrazolo[4,3-d]oxazolyl, 4H-imidazo[4,5-d]thiazolyl, pyrazino[2,3-d]pyridazinyl, imidazo[2,1-b]thiazolyl, cyclopenta[b]pyranyl, 4H-[1,3]oxathiole-[5,4-b]pyrrolyl, thieno[2,3-b]furanyl, imidazo[1,2-b][1,2,4]triazinyl and 4H-1,3-dioxolo[4,5-d]imidazolyl.

36. The method of Claim 35 wherein said angiotensin II receptor antagonist compound having said first-and-second-portion moieties of Formula I and II is further characterized by having an acidic moiety attached to either of said first-and-second-portion moieties.

37. The method of Claim 36 wherein said acidic moiety is attached to the first-portion moiety of Formula I and is defined by Formula III:

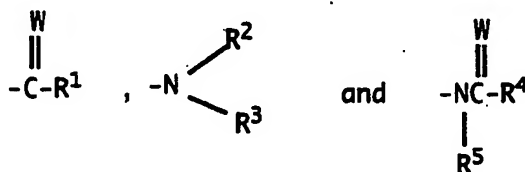


wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide,

ester and salt derivatives of said acidic moieties;  
 wherein U is a spacer group independently selected from  
 one or more of alkyl, cycloalkyl, cycloalkylalkyl,  
 alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one  
 5 or more ring atoms selected from oxygen, sulfur and  
 nitrogen atoms.

38. The method of Claim 37 wherein said acidic  
 moiety is selected from carboxyl moiety and tetrazolyl  
 10 moiety.

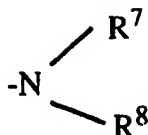
39. The method of Claim 37 wherein any of the  
 moieties of Formula I and Formula II may be substituted  
 at any substitutable position by one or more radicals  
 15 selected from hydrido, hydroxy, alkyl, alkenyl, alkynyl,  
 aralkyl, hydroxyalkyl, haloalkyl, halo, oxo, alkoxy,  
 aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl,  
 cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano,  
 cyanoamino, nitro, alkylcarbonyloxy, alkoxyalkoxyloxy,  
 20 alkylcarbonyl, alkoxyalkoxy, aralkoxyalkoxy,  
 carboxyl, mercapto, mercaptocarbonyl, alkylthio,  
 arylthio, alkylthiocarbonyl, alkylsulfinyl,  
 alkylsulfonyl, haloalkylsulfonyl, aralkylsulfinyl,  
 aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl  
 25 having one or more ring atoms selected from oxygen,  
 sulfur and nitrogen atoms, and amino and amido radicals  
 of the formula



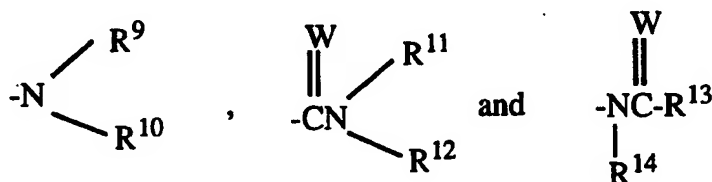
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wherein W is oxygen atom or sulfur atom; wherein each of  
 R<sup>1</sup> through R<sup>5</sup> is independently selected from hydrido,  
 alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, YR<sup>6</sup>  
 and

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wherein Y is selected from oxygen atom and sulfur atom and R<sup>6</sup> is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> is further independently selected from amino and amido radicals of the formula



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wherein W is oxygen atom or sulfur atom; wherein each of R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R<sup>2</sup> and R<sup>3</sup> taken together and each of R<sup>4</sup> and R<sup>5</sup> taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein each of R<sup>2</sup> and R<sup>3</sup> taken together and each of R<sup>7</sup> and R<sup>8</sup> taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido



radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

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40. The method of Claim 39 wherein said angiotensin II receptor antagonist is 5-[2-[5-[(3,5-dibutyl-1H-1,2,4-triazol-1-yl)methyl]-2-pyridinyl]phenyl-1H-tetrazole or a pharmaceutically-acceptable salt thereof and said epoxy-steroidal aldosterone receptor antagonist is 9 $\alpha$ -, 11 $\alpha$ -epoxy-7 $\alpha$ -methoxycarbonyl-20-spirox-4-ene-3,21-dione or a pharmaceutically-acceptable salt thereof.

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41. The method of Claim 40 further characterized by said angiotensin II receptor antagonist and said epoxy-steroidal aldosterone receptor antagonist being present in said combination in a weight ratio range from about one-to-one to about twenty-to-one of said angiotensin II receptor antagonist to said aldosterone receptor antagonist.

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42. The method of Claim 41 wherein said weight ratio range is from about five-to-one to about fifteen-to-one.

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43. The method of Claim 42 wherein said weight ratio range is about ten-to-one.

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44. The method of Claim 28 wherein said angiotensin II receptor antagonist is selected from the group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170,

EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,

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BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,

EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,

LY-235656, PD-150304, U-96849, U-97018, UP-275-22,

WAY-126227, WK-1492.2K, YM-31472, losartan potassium,  
E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,  
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,  
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,  
5 L-162441, L-163007, PD-123177, A-81988, BMS-180560,  
CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167,  
EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739,  
HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline,  
KRI-1177, L-158809, L-158978, L-159874, LR B087,  
10 LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970,  
RWJ-46458, S-8307, S-8308, saprisartan, saralasin,  
Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731,  
BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017,  
LY-301875, XH-148, XR-510, zolasartan and PD-123319.

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45. The method of Claim 44 wherein said  
angiotensin II receptor antagonist is selected from the  
group consisting of:

saralasin acetate, candesartan cilexetil, CGP-63170,  
20 EMD-66397, KT3-671, LR-B/081, valsartan, A-81282,  
BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194,  
EXP-3174, KW-3433, L-161177, L-162154, LR-B/057,  
LY-235656, PD-150304, U-96849, U-97018, UP-275-22,  
WAY-126227, WK-1492.2K, YM-31472, losartan potassium,  
25 E-4177, EMD-73495, eprosartan, HN-65021, irbesartan,  
L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan,  
UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234,  
L-162441, L-163007 and PD-123177.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/09335

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K45/06 A61K31/585 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.              |
|------------|---|------------------------------------|
| P,X        | WO,A,95 15166 (CURATORS OF THE UNIVERSITY OF MISSOURI) 8 June 1995  | 1-5,<br>19-21,<br>28-32            |
| P,A        | see page 6, paragraph 3<br>see page 8, paragraph 3 - page 10,<br>paragraph 3; claims 1-3,5<br>see page 14, paragraph 2<br>see page 19, paragraph 3<br>--- | 13,24,40                           |
| Y          | WO,A,94 09778 (MERCK & CO, INC) 11 May 1994<br><br>see page 4-6; claims 1,2,6,7<br>---<br>-/--  | 1-12,<br>17-21,<br>28-39,<br>44,45 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*A\* document member of the same patent family

Date of the actual completion of the international search

6 November 1996

Date of mailing of the international search report

20. 11. 96

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Kanbier, D

## INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/US 96/09335

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.              |
|------------|---|------------------------------------|
| Y          | THE JOURNAL OF STEROID BIOCHEMISTRY,<br>vol. 32, no. 1B, 1989,<br>pages 223-227, XP000607722<br>DE GASPARO ET AL: "ANTIALDOSTERONES:<br>INCIDENCE AND PREVENTION OF SEXUAL SIDE<br>EFFECTS "  | 1-12,<br>17-21,<br>28-39,<br>44,45 |
| A          | see page 223, right-hand column<br>see page 225<br>see page 226, right-hand column<br>---   | 13,24,40                           |
| A          | THE JOURNAL OF PHARMACOLOGY AND<br>EXPERIMENTAL THERAPEUTICS,<br>vol. 240, no. 2, 1987,<br>pages 650-656, XP000607709<br>DE GASPARO ET AL: "THREE NEW<br>EPOXY-SPIROLACTONE DERIVATIVES:<br>CHARACTERIZATION IN VIVO AND IN VITRO"<br>see page 650<br>see page 653, left-hand column<br>see page 654<br>--- | 1-5,13,<br>19-21,<br>24,28-32      |
| A          | EP,A,0 122 232 (CIBA-GEIGY AG) 17 October<br>1984<br><br>see page 2 - page 6, paragraph 1<br>see page 21, paragraph 2 - page 23,<br>paragraph 2; claims 1-8,10; example 17<br>-----   | 1-5,13,<br>19,20,<br>24,28-32      |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/ 09335

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-45  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 19-27, 28-45  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
Claims searched incompletely: 1-4, 6-12, 17-19, 22, 23, 33-39, 41, 44, 45  
Please see next page.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 09335

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

In view of the large number of compounds, which are defined by the general formula(e)/description, used in claim(s) 2-4,6-12,17,18,29-31,33-39,44,45, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, part B, chapter III, paragraph 3.6).

Meaningful search not possible on the basis of all claims:

A compound cannot be sufficiently characterized by its pharmacological profile or its mechanism of action as it is done in Claims 1,19,22,23 and 41 as: "angiotensin II receptor antagonist" and aldosterone receptor antagonist". In this context, the search has been executed based on compounds specifically mentioned in Claims 5,13,17,18,24,32,40,44 and 45.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/09335

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| WO-A-9515166                              | 08-06-95            | US-A- 5529992              | 25-06-96            |
|   |                     | AU-A- 1210695              | 19-06-95            |
|   |                     | CA-A- 2177848              | 08-06-95            |
|   |                     | EP-A- 0730458              | 11-09-96            |
| -----                                     |                     |                            |                     |
| WO-A-9409778                              | 11-05-94            | AU-A- 5449194              | 24-05-94            |
| -----                                     |                     |                            |                     |
| EP-A-122232                               | 17-10-84            | AU-B- 565017               | 03-09-87            |
|   |                     | AU-A- 2685384              | 18-10-84            |
|   |                     | CA-A- 1220781              | 21-04-87            |
|   |                     | DE-A- 3475622              | 19-01-89            |
|   |                     | JP-C- 1586804              | 19-11-90            |
|   |                     | JP-B- 2012479              | 20-03-90            |
|   |                     | JP-A- 59231100             | 25-12-84            |
|   |                     | US-A- 4559332              | 17-12-85            |
| -----                                     |                     |                            |                     |

